THE DIAGNOSIS, TREATMENT AND PREVENTION OF CAPD PERITONITIS

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This thesis is dedicated to Rosamond, Nana and Lorna - mother, wife and daughter.

CONTENTS

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ABSTRACT

Introduced in 1976, continuous ambulatory peritoneal dialysis (CAPD) is an effective and increasingly popular form of long-term dialysis. Infective peritonitis is its main drawback. This can be caused by a wide variety of micro-organisms, but usually by bacteria from the skin or gut. The commonest and most troublesome causative organism is the coagulase-negative staphylococcus. Although improvements in methods of diagnosis, treatment and prevention were made during the first five years of its use, CAPD continued to be plagued by peritonitis in most centres.

This study was carried out between 1982 and 1984 in the Queen Elizabeth Hospital, Birmingham. A CAPD service began there in 1981 and peritonitis quickly became the main threat to its success. It was soon evident that the methods then in use for the microbiological diagnosis of CAPD peritonitis were inadequate. A simple method of culture was developed which greatly increased the chances of a positive microbiological diagnosis. This method became the cornerstone of a more effective and economical laboratory service to the CAPD programme.

The antibiotic sensitivities of organisms causing CAPD peritonitis were studied with the aim of establishing a more effective initial treatment policy. Vancomycin was found to be the most consistently active of the antibiotics tested against Gram positive isolates in general and the coagulase-negative staphylococcus in particular. Aminoglycosides were the most consistently active against Gram negative isolates. A trial of intra-peritoneal vancomycin and tobramycin showed that this combination was much more effective in the initial treatment of

CAPD peritonitis than cefuroxime, previously the antibiotic of first choice. However, potentially ototoxic levels of tobramycin were encountered.

With the aim of making initial treatment both simpler and safer, a modified protocol involving once-daily intra-peritoneal vancomycin and gentamicin was developed. One hundred episodes of CAPD peritonitis were treated, of which 88 were cured without recourse to other antibiotics. This study showed for the first time that most episodes of CAPD peritonitis could be safely treated at home using intra-peritoneal antibiotics self-administered once-daily. The problem of aminoglycoside toxicity was not solved, however.

Many episodes of CAPD peritonitis follow contamination of the administration set with organisms on the patient's hands. Contamination usually occurs during the dialysate exchange procedure. We studied how effectively bacteria were removed from the patients' hands by washing with povidone iodine detergent or 70% ethyl alcohol. Surprisingly, povidone iodine was often found to be counter-productive. Ethyl alcohol was much more effective and convenient.

Despite improvements in the diagnosis and treatment of CAPD peritonitis, its incidence at the Queen Elizabeth Hospital has recently increased. This may in part be due to a steady decline in the amount of time staff can devote to training and supervising individual patients: staffing of the programme has failed to keep pace with the rapid rise in patient numbers. The thesis ends with a review of a variety of recently developed techniques and strategies which aim to prevent CAPD peritonitis.

INTRODUCTION

"All progress is precarious and the solution of one problem brings us face to face with another problem."

Martin Luther King jnr

Until around thirty years ago, chronic renal failure was as fatal as rabies, only less hurriedly so. Then haemodialysis made its faltering debut and the next decade saw the first tentative experiments in human renal transplantation. These techniques have since been progressively refined and as a result, most patients with chronic renal failure should, in principle, be able to elude death for many years. Unfortunately, however, both haemodialysis and transplantation are expensive and highly sophisticated techniques. Their application has been restricted in most countries by limited dialysis facilities and an inadequate supply of kidneys suitable for transplantation. Many patients, and especially those over 60 years of age, have thus been denied treatment. Furthermore, haemodialysis in particular offers its recipients a way of life which falls far short of the ideal. For example, patients must spend many hours each week attached to their dialysis machines; they must submit to a very restricted diet and fluid intake; they are subject to wild swings in body biochemistry resulting in major fluctuations in their sense of well-being.

It was against this imperfect background that continuous ambulatory peritoneal dialysis (CAPD) was launched in 1976. CAPD seemed to avoid many of the difficulties inherent in haemodialysis.

It dispensed with the need for regular attachment to a machine; it provided continuous rather than fluctuant control of blood biochemistry; it permitted a much more liberal diet and fluid intake; it required a minimal capital outlay and promised to be cheaper to run than haemodialysis. It also nicely matched the mood of an American (and later British) public, keen to embrace any type of therapy which seemed less dehumanising than the high technology medicine which was seen as dominating health care.

CAPD quickly became established as a major form of dialysis and in many centres in the United Kingdom and North America it became the dialysis technique of choice. However, CAPD has one major drawback. Because the technique requires the creation and maintenance of an artificial communication between the peritoneum and the exterior, the CAPD patient is constantly haunted by the spectre of infective peritonitis. When it strikes, peritonitis can threaten the success of the dialysis technique and, if inadequately treated, place the patient's very survival at risk.

Man has suffered from peritonitis since the beginning of history. It is usually caused by some intra-abdominal catastrophe leading to the leak of gastro-intestinal or genito-urinary contents into the peritoneum. As a rule, its course is violent and ultimately fatal unless both the infection and the underlying disorder can be corrected. CAPD peritonitis, on the other hand, is only as old as CAPD itself and differs in many respects from classical peritonitis. Consequently, it has presented new problems of diagnosis, treatment and prevention, the solutions of which have proved surprisingly elusive.

All dialysis centres using CAPD have had to deal with an epidemic of CAPD peritonitis. This thesis starts by outlining the scale and nature of this iatrogenic scourge and the attempts to master it which were made during the first five years of CAPD. It then describes the work I carried out with the renal unit at the Queen Elizabeth Hospital, Birmingham, between 1982 and 1984. We attempted to rationalise our methods of diagnosing peritonitis; develop treatment that was effective, safe, convenient and cheap; and explore the problem of prevention. As the reader will discover, we were thus able to tame the beast without persuading it to go away. The thesis finishes with an examination of the methods currently under development which hold the most promise of peritonitis-free CAPD.

On the surface. this thesis is about dialysate, bacteria and antibiotics. At bottom, however, it describes a small part of a major world-wide effort to secure a healthier and happier future for those of us unfortunate enough to lose the use of our kidneys.

PROLOGUE

CAPD PERITONITIS

FIVE YEARS IN THE WORLD, ONE YEAR IN BIRMINGHAM

1. What is CAPD?

The birth of continuous ambulatory peritoneal dialysis (CAPD) was announced without ostentation in an abstract submitted to the American Society for Artificial Internal Organs by Popovich et al in 1976. The infant was initially called "the equilibrium peritoneal dialysis technique" but two years later its progenitors rebaptised it with the name by which it is now known (Popovich et al, 1978). In brief, two litres of dialysate were infused into the peritoneal cavity via a permanent intraperitoneal catheter and left there for four to five hours. The dialysate was then drained and replaced. There were five dialysate exchanges per day, seven days per week. The two radically new features of this technique were firstly that while dialysis was in progress patients could pursue their normal activities; and secondly that because dialysis was virtually continuous, biochemical stability could be achieved.

CAPD is the first-born of the third generation of peritoneal dialysis techniques. Peritoneal dialysis relies on the fact that substances of relatively low molecular weight can diffuse from the blood across the peritoneal membrane into fluid instilled into the peritoneal cavity. The first member of this therapeutic dynasty was developed by Ganter in 1923 (Boen 1981). He instilled 1.5

litres of saline solution into the peritoneal cavity of a patient with uraemia. Over the next forty years, the technique was used more and more widely to treat patients in acute renal failure. During the first two decades, patients treated with peritoneal dialysis rarely recovered but, thereafter, survival rates gradually improved. This was due to the development of more reliable intraperitoneal catheters, to improvements in the composition and use of the dialysate and to more successful prevention and treatment of peritonitis. Peritoneal dialysis remains a standard treatment for acute renal failure.

In the late fifties and early sixties, Boen (1961) and Tenckhoff (1965) calculated and then confirmed in practice that if the volume and flow of dialysate were sufficiently high, peritoneal dialysis could be used for the long term treatment of patients in chronic renal failure. However, their first attempts using a permanent intraperitoneal catheter all failed due to peritonitis or catheter blockage. A major advance was made by Tenckhoff and Schecter (1968) who developed an intraperitoneal catheter made of silicon rubber. The intraperitoneal portion was 20 cm long and perforated with many holes to reduce the chance of blockage. The extraperitoneal portion was designed to lie within a subcutaneous tunnel some 12 cm long. Dacron cuffs were attached to the catheter just below the skin and just outside the peritoneum. These improved the catheter seal, preventing the leakage of dialysate from the distended peritoneum and, crucially, the passage of micro-organisms from the skin into the peritoneum. This catheter, now called the Tenckhoff catheter, proved to be suitable for long term use and made chronic intermittent peritoneal dialysis a practical proposition. Patients were treated for ten to twelve hour periods two to three times each week. While dialysing, they had to remain attached to a machine which instilled and drained the dialysate in a controlled manner. Peritonitis still occasionally occurred, as did other complications such as dialysate leaks, catheter blockage and abdominal pain. Also, some patients could not be adequately dialysed by this method. Consequently, in the eyes of many nephrologists, chronic intermittent peritoneal dialysis seemed less suitable than haemodialysis for most patients and now accounts for only a very small proportion of dialysis patients in most countries.

Intermittent peritoneal dialysis had shown, however, that the peritoneal membrane could be used as an artificial kidney for long periods. The key step that led to the development of CAPD was the recognition by Popovich and his colleagues that once the dialysate was instilled into the peritoneum, the patient could be detached from the dialysate source. Satisfactory dialysis could continue for several hours before blood and dialysate concentrations began to equilibrate. If the dialysate was replaced every four or five hours and was continued every day, the improvement in blood biochemistry proved to be comparable to that achieved by haemodialysis. However, unlike haemodialysis, CAPD, being continuous, resulted in the achievement of a steady biochemical state.

Following their initial announcement of the technique in 1976, Popovich and his colleagues reported in 1978 on its use in nine patients. They found that CAPD could control blood biochemistry at least as well as could other dialysis techniques. They were also impressed by the considerable improvement in the sense of well-being experienced by the patients and by their enthusiasm for the freedom the technique allowed. Many patients became appreciably more active than they had been on haemodialysis or intermittent peritoneal dialysis.

The major complication of CAPD that they encountered was bacterial peritonitis. Thirteen episodes occurred during the 138 patient-weeks of the study, or about one episode every ten patient-weeks. Organisms commonly found on the skin were usually responsible and included staphylococci, streptococci, an acinetobacter and an **Enterobacter cloacae.** All episodes were said to have responded rapidly to antibiotics added to the dialysate. The authors felt that most episodes of peritonitis followed contamination of the dialysate during the dialysate exchange procedures.

A description of the technique of dialysate exchange makes the risk of contamination easy to understand. In between exchanges, the patient's Tenckhoff catheter was sealed with a cap. To begin the exchange, the patient removed the cap and attached the catheter to a plastic infusion line leading to an empty two litre glass bottle. The bottle was placed on the ground and the dialysate effluent was allowed to drain from the peritoneum into the bottle. When the drainage was complete, the bottle was replaced with one containing fresh dialysate which was then instilled into the peritoneum. Finally, the bottle and infusion line were disconnected from the catheter which was resealed with a sterile cap. Thus, the system was opened three times during each exchange, and hence, with five exchanges daily, 105 times each week. Even assuming that all episodes of peritonitis were caused by contamination during the dialysate exchange, an incidence of one episode every ten weeks would occur if the dialysate was contaminated only once in every 1,000 times the system was opened.

The incidence of peritonitis seems in fact creditably low in the face of the technique's extreme vulnerability to contamination. This is particularly so when "many patients changed fluids in automobiles, parks or restrooms so that they did not need to return home at inconvenient times" (Popovich et al, 1978). Thus, the freedom offered by CAPD compared with other forms of dialysis was offset by the need for patients to devote the utmost care to their fluid exchanges. It was apparent from the outset that CAPD could only succeed if patients were thoroughly trained in the technique of aseptic fluid exchange and were seen to be capable of achieving this before they were allowed home. Such training remains an integral part of all CAPD programmes to this day.

Major progress towards reducing the risk of peritonitis was made by Oreopoulos and his colleagues in 1978 when they replaced the glass bottles with collapsible plastic bags (Figure P.1). Now, instead of removing the bottle and administration tubing and capping the catheter, the bag and tubing could be left attached to the catheter, rolled up and kept in a pouch until the next exchange. This meant that the system was opened only once at each exchange. It was also found that most patients could be adequately dialysed using four and occasionally only three exchanges daily. Together, these modifications reduced the number of disconnections

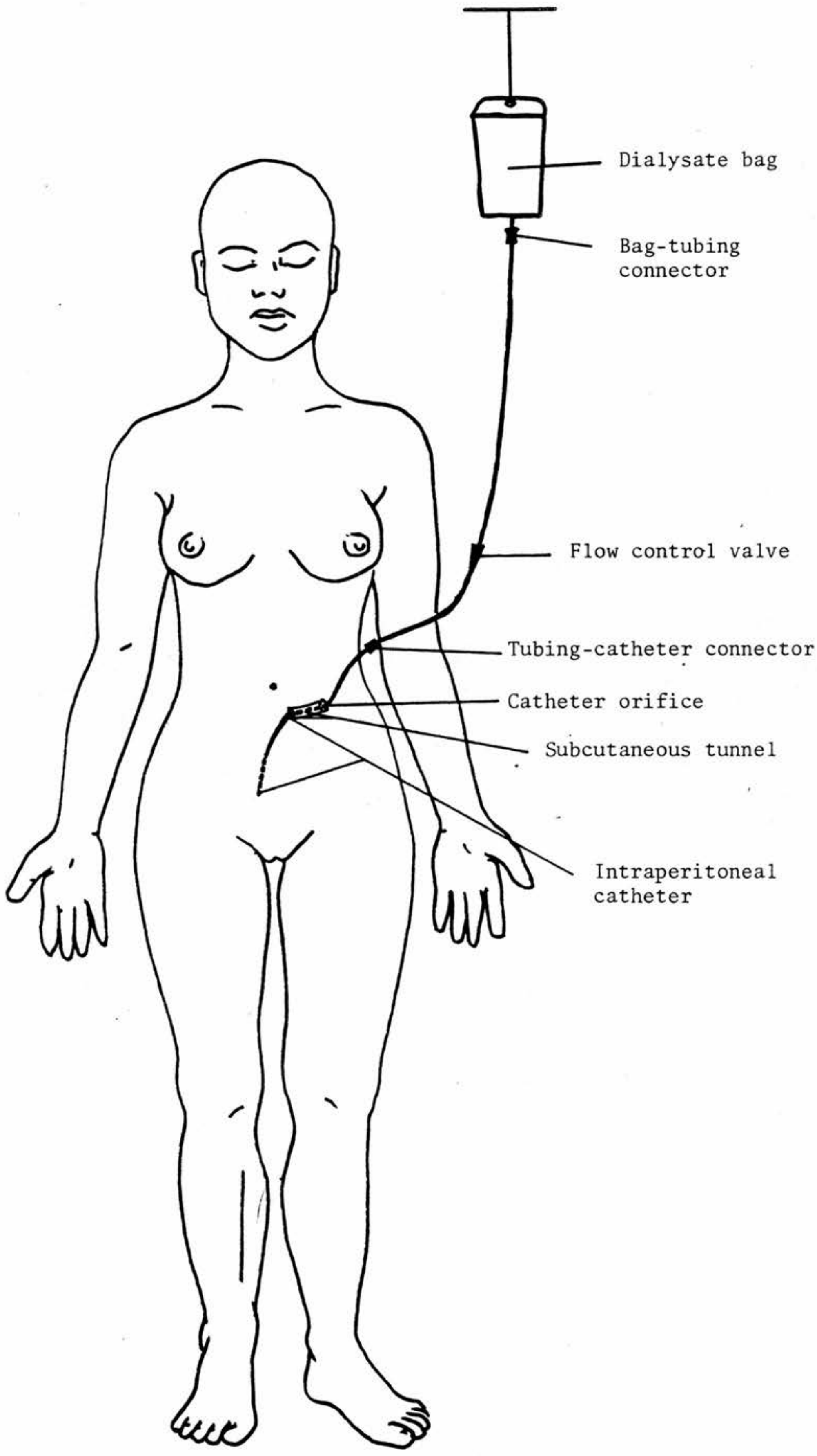

Figure P.1 CAPD dialysate inflow

per week from 105 to 28. Another important cause of contamination then emerged: accidental disconnection of the administration tubing from the Tenckhoff catheter. This was solved by the introduction of a titanium connector which provided a very secure seal between the catheter and the tubing (Oreopoulos et al, 1981).

The result of these modifications was substantially to reduce the incidence of peritonitis. The Toronto group, headed by Dimitrios Oreopoulos, reported an incidence of one episode every 7.9 months in 1978 (Williams, 1981). With the apparent taming of peritonitis, CAPD suddenly became a much more attractive proposition and the message was broadcast with missionary zeal by the pioneers in Texas and Toronto. CAPD was seen to be particularly suitable for elderly and diabetic patients and others with cardiovascular disease for whom haemodialysis was not a practical proposition. CAPD also seemed likely to cost less than haemodialysis. Virtually no capital outlay is required to start a CAPD service, the main costs being incurred in the provision of the dialysate and in staff salaries. Thus, for health authorities eager to cut costs, the arguments in favour of CAPD were also seductive. Consequently, 1978-80 saw a remarkable growth in the number of patients using CAPD in North America, Europe and Australasia. For example, in the United States, it increased from 20 in 1977 to 1,700 three years later (Moncrief and Popovich, 1981a). Between 1978 and 1980, 219 patients were trained in CAPD in Australia (Thompson et al, 1981) and 325 in the United Kingdom (Gokal and Ward, 1981).

By 1980, several centres had accrued considerable experience in CAPD. The leading exponents of the technique from three continents assembled in Melbourne in the autumn of that year for a major re-appraisal of CAPD in the light of this experience. The proceedings of this conference (Atkins et al, 1981a) and several other contemporaneous publications made it abundantly clear that peritonitis remained the main threat to successful CAPD despite the technical improvements that had been made. In the following sections, I shall describe the problem of CAPD peritonitis in more detail. Emphasis will be placed on the difficulties of diagnosis and treatment which still remained in 1981 when the CAPD programme with which I was associated began.

2. The Incidence of Peritonitis

Table P.1 shows the incidence of peritonitis reported by ten CAPD centres, expressed as months of CAPD per episode. While in most centres the average was about one to two episodes per patient per year, there was a remarkable ten-fold difference between the highest and lowest incidences. A number of factors may account for this.

Technical improvements undoubtedly play an important part. The dramatic fall in the incidence at Centre 1 from one episode every two months to one every seventeen months coincided with their changing from glass bottle to plastic bags. However, plastic bags and equipment provided by the same firm, Travenol Laboratories, were used by most centres from 1978 onwards, suggesting that other factors are also important. Centre 7 in Toronto reduced its incidence of peritonitis appreciably from 1979 to 1980 without introducing any major technical changes (Table P.1) (Oreopoulos et

TABLE P.1

INCIDENCE OF CAPD PERITONITIS REPORTED BY 10 CENTRES DURING 1977-1981

Authors		Date	Country	Patient-Months	Months/Episode
1a	Rubin et al	1980	United States	185	2
2	Atkins et al	1981	Australia	1,090	3.5
3	Gokal et al	1980	United Kingdom	138	5
4	Chan et al	1981	United Kingdom	497	5.5
5	Lindholm et al	1981	Sweden	242	7
6	Lameire et al	1981	Belgium	673	7.5
7a	Williams et al	1978	Canada	776	8
8	Morrison et al	1981	New Zealand	?	8
9	Mergerion et al	1981	West Germany	375	8.6
7b	Williams et al	1979	Canada	1,588	9.2
7c	Williams et al	1980	Canada	1,797	13.3
1b	Prowant et al	1981	United States	?	17
10	Mion et al	1981	France	715	20

al, 1981). Could patient selection and training play a part? Many authors noted that the incidence of infection was not evenly spread among their patients. C. Williams and her colleagues (1981) found that 44% of 315 patients had never had peritonitis, including many who had been using CAPD for more than one year. On the other hand, 59% of all episodes occurred in only 18% of the patients, with a "hard core" of 6% of patients experiencing 25% of all episodes. Fenton et al (1981) asked their nursing staff to assess the degree of co-operation shown by each patient. Whilst stressing they did not wish to attach too much importance to such a subjective evaluation, they nevertheless found that 80% of the patients who had three or more episodes of peritonitis were considered "unco-operative" compared with only 10% of patients who had had no peritonitis. Oreopoulos et al (1981b) felt that poor dialysate exchange technique probably led to peritonitis in 46% of 93 episodes and possibly in a further 26%. They concluded that motivation and cleanliness were key factors in determining a patient's risk of developing peritonitis and should be taken into account when assessing his or her suitability for CAPD. Moncrief and Popovich (1981b) stated that patients in their centre who had more than three episodes of peritonitis within the first six months were advised to change to haemodialysis where practicable. Criteria for acceptance for and removal from a CAPD programme will clearly vary from centre to centre as will the quality of the training offered to patients. It is inevitable that the incidence of peritonitis will be influenced by these factors.

The centre reporting the lowest incidence of peritonitis

(Mion et al, 1981) was the only one where a bacterial filter was placed in the administration line between the bag and the Tenckhoff catheter to prevent bacteria introduced during the bag exchange from reaching the peritoneum (Figure P.2) (Slingeneyer et al, 1981). After excluding episodes caused by accidental disconnection of the administration tubing from the catheter, they calculated that the incidence of peritonitis at their centre was only one episode every 31 patient months. They cultured 114 filters used by 16 patients, each worn for 10 to 14 days. Organisms were isolated from the bag side of the filter in 25%, but from the catheter side in only 3%. Most of the isolates belonged to species known to cause CAPD peritonitis. It thus seemed plausible that the filter was preventing peritonitis, although no attempt was made to compare the incidences of CAPD peritonitis with and without the filter. However, in an earlier long-term study on patients using intermittent peritoneal dialysis, they found that the incidence of peritonitis was equally low - one episode every 4.7 patient years - whether or not the filter was used. Consequently, they were unable to provide unequivocal evidence that the use of the filter was the key to their success.

The incidence of peritonitis in a given CAPD centre is undoubtedly multifactorial in origin. As things stood at the end of 1981, the principal onus lay upon the patient to carry out his or her dialysate exchanges precisely as instructed. It was clear that until technical modifications removed the risk of patient error, CAPD peritonitis would continue to occur.

Whilst many authors attributed most episodes of peritonitis to contamination occurring during the dialysate exchange or to

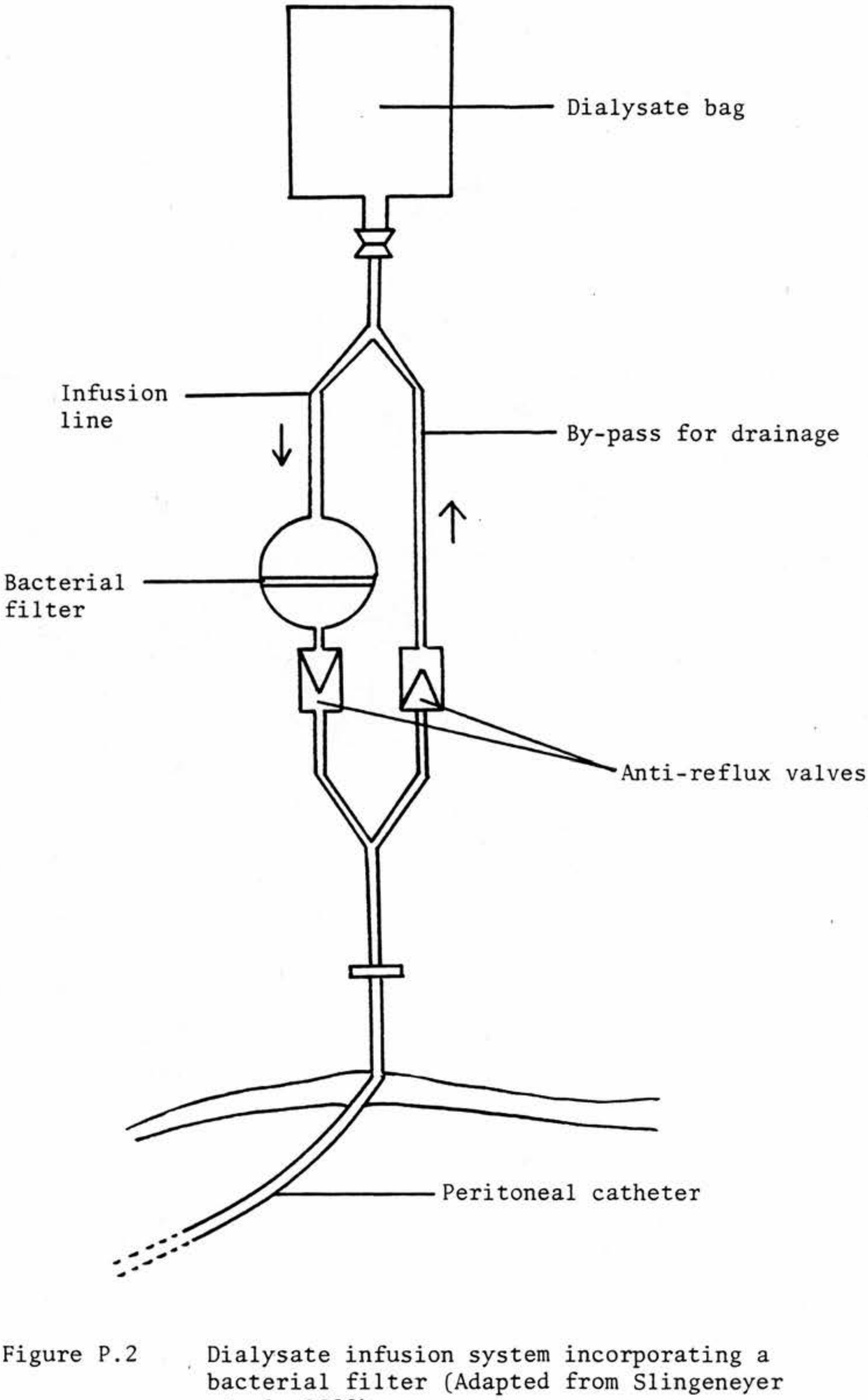

Figure P.2 Dialysate infusion system incorporating a bacterial filter (Adapted from Slingeneyer et al, 1982) accidental disconnection of the administration tubing from the Tenckhoff catheter, several other sources of infection were mentioned. These included infection of the Tenckhoff catheter exit site; cracks or holes in the administration tubing or dialysate bag; leak of bowel contents via an intestinal perforation; and blood-borne oral organisms. These will be considered in more detail in later sections.

3. The Clinical Presentation of CAPD Peritonitis

CAPD peritonitis is usually easy to diagnose. Uninfected dialysate effluent is normally crystal clear with a yellowish tinge. Its white cell content is low. For example, the white cell content of 149 samples of uninfected dialysate ranged from 0-85/mm^3 with a mean of 23/mm^3 (Prowant and Nolph, 1981). Peritonitis usually results in a rapid rise in the dialysate white cell count to at least 300/mm^3 (Rubin et al, 1980). A white cell count of more than 100/mm^3 results in the dialysate becoming visibly cloudy (Moncrief and Popovich, 1981b). Cloudy dialysate effluent is thus the cardinal feature of CAPD peritonitis.

The clinical features at presentation in two studies covering 259 episodes of peritonitis are shown in Table P.2. In two-thirds of the episodes, the patient complained only of cloudy effluent with or without abdominal pain. The two main determinants of the patient's clinical state when first seen by a doctor were (1) the duration of the infection and (2) the causative organism. What began as a symptomless condition, evident only as a "cloudy bag", would progress to one of increasingly severe abdominal pain

TABLE P.2

SYMPTOMS AT PRESENTATION IN 259 CASES OF CAPD PERITONITIS

	Principal Author		
	Nolph (1981) N = 110 %		Fenton (1980) N = 149 %
Cloudy dialysis effluent	97		99
Abdominal pain or discomfort	86	$\rho < 0.01$*	97
Pyrexia	29		35
Nausea or vomiting	20	$\rho < 0.02$*	35
Chills	16		23
Drainage problems	15		?
Diarrhoea	?		7

* X^2 with Yates' correction

accompanied by the other familiar symptoms of bacterial peritonitis - nausea and vomiting, fever, hypotension and collapse. It is notable that symptoms were more often severe in the cases studied by Fenton and his colleagues (Table P.2) perhaps suggesting that their patients took longer to seek medical attention.

Because peritonitis is such a frequent and potentially serious complication of CAPD, all CAPD patients are instructed to report to their CAPD centre as soon as the dialysate becomes cloudy or other symptoms suggesting peritonitis develop. Consequently, patients should rarely be seriously ill when first seen. The relationship between the nature of the causative organism and the clinical condition of the patient will be discussed in the next section.

4. The Organisms Causing CAPD Peritonitis

By the end of 1981, a number of CAPD centres had published details of the micro-organisms they had found to cause peritonitis in their patients. The findings of nine centres from seven countries and covering 843 episodes of CAPD peritonitis are summarised in Table P.3. Several features are immediately apparent:-

(1) A very similar range of organisms was found to cause peritonitis in North America, Europe and Australasia;

(2) The majority of causative organisms were Gram positive cocci with the commonest single species in most centres being **Staphylococcus epidermidis**;

(3) In only two centres, both in North America, were anaerobes recovered;

TABLE P.3

CULTURE RESULTS IN 843 EPISODES OF CAPD PERITONITIS

	Principal Author									
Organism	Rubin 1980	Lameire 1981	Prowant 1981	Vas 1981	Moncrief 1981	Atkins 1981c	Chan 1981	Mergerian 1981	Lindholm 1981	Total (%)
Coagulase-negative staphylococci	30	58	35	47	5	38	21	16	7	257 (39)
Staphylococcus aureus	10	22	26	10	6	12	4	16	7	113 (17)
Streptococcus spp	11	12	14	16	4	25	10	9	0	101 (15)
Diphtheroids	0	2	2	0	0	9	0	0	0	13 (2)
Enterobacteriaceae		15	12	14	1	6	15		0	
Pseudomonas spp	15	7	7	5	2	0	2	2	0	112 (17)
Acinetobacter spp		1	2	0	0	3	3		0	
Anaerobic organisms	0	0	0	4	1	0	0	0	0	5 (0.8)
Fungi	2	1	5	7	0	0	0	2	0	17 (2.6)
Other	3	7	5	3	0	11	0	0	4	33 (5)
Total	71	125	108	106	19	104	55	45	18	651
Culture negative (%)	26 (27)	36 (22)	31 (22)	4 (4)	1 (5)	50 (32)	37 (40)	2 (4)	7 (28)	194 (23)

(4) In most centres, organisms were not recovered in 20 to 40% of episodes whilst in three, organisms were isolated in all but 4% of episodes.

The causative organisms can be considered in four groups:-

(1) Resident skin flora;

(2) Transient skin flora;

(3) Organisms of intestinal origin;

(4) Organisms of uncertain origin.

Resident skin flora: Staph. epidermidis, a coagulase-negative staphylococcus, was incriminated in 39% of the culture-positive episodes, more than twice as often as any other organism. The taxonomy of the coagulase-negative staphylococci has undergone major changes during the past decade (Kloos and Schleifer, 1975). Previously, the name **Staph. epidermidis** or **Staph. albus** had been generally applied to all coagulase-negative staphylococci. Subsequently, however, the definition of **Staph. epidermidis** became much more precise and a number of other species of coagulase-negative staphylococci were recognised. As none of the authors of the reports summarised in Table P.3 defined what they meant by **Staph. epidermidis,** it cannot be accepted that all the isolates were **Staph. epidermidis, sensu stricto.** For the moment, these organisms will be described as coagulase-negative staphylococci. Their true identity will be discussed in Chapter 3.

Coagulase-negative staphylococci are constant residents of the human skin and in normal circumstances do not cause infection. During the past fifteen years, however, they have been shown to cause low-grade infections subsequent to their colonisation of inert material, particular plastics, used as intravascular catheters, prosthetic joints, heart valves, cerebrospinal fluid shunts etc (Lowy and Hammer, 1983). It thus comes as no surprise that they should cause peritonitis in a plastic system which is vulnerable to contamination with skin organisms several times each day. Peritonitis due to coagulase-negative staphylococci was generally found to be a mild condition with abdominal pain being the only major symptom at presentation (Oreopoulos, 1981b).

Other skin commensals were rarely isolated from infected dialysate. Diphtheroids were isolated in 13 of the 843 episodes (1.5%). Nine of these episodes occurred in one centre which employed a variety of culture methods requiring complex manipulation (Atkins et al, 1981b). Human skin diphtheroids have rarely been implicated in human infection (Noble, 1984). Their role in these episodes must therefore remain uncertain. **Acinetobacter calcoaceticus** was isolated on nine occasions (1%). This organism is found on the skin of about 10% of the population (Gill and Gill, 1979). In recent years, it has been shown to cause septicaemia and infection of burns and surgical wounds, particularly in patients who are debilitated or have received broad spectrum antibiotics. The source of septicaemia is often found to be a colonised intravascular catheter. **Acinetobacter calcoaceticus** is therefore an organism of known pathogenic potential in the circumstances created by CAPD.

Transient skin organisms: Staphylococcus aureus was found to cause CAPD peritonitis in all nine centres and accounted for 17% of all isolates. Unlike the coagulase-negative staphylococci, **Staph. aureus** is not a permanent resident of the skin. It colonises the anterior nares of 8 to 30% of adults but is generally found on the skin of less than 5% (Smith, 1981). No data concerning the percentage of CAPD patients colonised with **Staph. aureus** were available in 1981. However, Vas (1981) noted that patients with **Staph. aureus** peritonitis often had a concurrent **Staph. aureus** infection of the catheter exit site which could act as source of recurrent peritonitis until eradicated. Whether the infecting organisms in such cases reached the peritoneum by making their way down the outside of the Tenckhoff catheter or by contamination of the fluid during the bag exchange had not been established.

Predictably, this relatively virulent organism often caused more severe peritonitis than did coagulase-negative staphylococci. Vas (1981) found that dialysate infected with **Staph. aureus** usually had a high white cell and fibrin content and patients required a long course of treatment, often culminating in removal of the intraperitoneal catheter. Oreopoulos et al (1981b) believed that peritonitis due to **Staph. aureus** required more intensive treatment than that caused by most other organisms. Atkins et al (1981c) reported that patients with **Staph. aureus** peritonitis were febrile and remained in hospital for longer than those with coagulase-negative staphylococcal peritonitis.

Organisms of bowel origin: All centres reported isolating **Enterobacteriaceae** from infected dialysate (Table P.3). These included **Escherichia coli, Proteus** spp, **Enterobacter cloacae** and **Serratia marcescens.** As a percentage of total isolates, they ranged from 6% (Atkins et al, 1981c) to 27% (Chan et al, 1981). Four centres also reported isolating **Streptococcus faecalis** (Vas et al, 1981a, Atkins et al, 1981c, Chan et al, 1981, Mergerian, 1981). These organisms are all part of the bowel flora but can also be found transiently on the skin especially of the groin, lower abdominal wall and hands (Sandusky, 1979). Peritonitis could thus follow either external contamination or leakage of bowel contents directly into the peritoneal cavity. The latter route would be especially probable if a mixed intestinal flora, including anaerobes was found. Vas et al (1981), one of only two groups to isolate anaerobes, reported several cases of "faecal peritonitis" in patients on CAPD who were found to have severe diverticular disease.

Organisms of uncertain origin: Pseudomonas: Most centres reported isolating members of this genus from infected dialysate but none made it clear if species other than **Pseudomonas aeruginosa** were involved. All the pseudomonads are normal inhabitants of water, vegetation and moist soil (Sanford, 1979). They rarely cause human infection except for **P. aeruginosa** which is an important cause of infection in debilitated patients in hospital. **P. aeruginosa** can be found in the nose, throat or faeces of 5 to 9% of healthy individuals (Cross, 1979). It is very readily isolated from sinks, damp cloths, mops, etc, and can also survive and multiply in a wide range of antiseptics and "sterile" fluids such as dialysate and distilled water. As CAPD patients necessarily spend a lot of time hand-washing and using antiseptics, there is a high chance their hands will occasionally become contaminated with pseudomonads. A subsequent technical error during a bag exchange would then allow the organism to enter the system.

Streptococci other than enterococci: All centres reported isolating streptococci from infected dialysate. Five did not identify them any further. Atkins et al (1981c) found that 21 of 25 isolates were viridans streptococci (**Strep. mitior** 14; **Strep. milleri** 2; **Strep. mutans** 2; and haemolytic streptococci 3), three were **Strep. faecalis** and one a microaerophilic streptococcus. Of their 16 streptococcal isolates, Vas et al (1981a) found ten were viridans streptococci and six were **Strep. faecalis**. Mergerian (1981) reported isolating seven "haemolytic" streptococci and two **Strep. faecalis** and Chan et al (1981) isolated two viridans streptococci. Oreopoulos et al (1981b) found that patients with viridans streptococcal peritonitis were often acutely ill at presentation. Fenton et al (1981) described two fatal cases of CAPD peritonitis, one caused by **Strep. pneumoniae**, the other by **Strep. agalactiae**.

Streptococci other than **Strep. faecalis** are rarely found on the skin, but transient viridans streptococcal bacteraemia occurs throughout the day in the course of chewing or tooth brushing (Durack, 1979). This bacteraemia is believed to lead to a large proportion of cases of infective endocarditis. Vas (1980) therefore suggested that most episodes of peritonitis caused by viridans streptococci resulted from organisms borne in the blood from the mouth to the peritoneal cavity. A similar mechanism was recently proposed to explain the rare association between pneumococcal peritonitis and intra-uterine contraceptive devices (Gruer et al, 1983).

Fungi: Five of the nine centres reported CAPD peritonitis due to organisms described as fungi or yeasts. Rubin et al (1980) reported two cases of peritonitis caused by **Candida albicans** and one by **Nocardia asteroides** (strictly speaking, a branching bacterium and not a fungus). They noted that the dialysate white cell count in these cases was lower than in those caused by bacteria. In one of the cases due to **C. albicans**, there was a very heavy growth of the organism but only 15 leukocytes/mm^3 in the dialysate. They contrasted this with a case due to **P. aeruginosa** where the dialysate white cell count was 14,400/mm^3 but only 2.5 bacteria/ml were present. Prowant and Nolph (1981) found that fungal CAPD peritonitis often produced a number of non-specific symptoms, days or even weeks before the dialysate became cloudy. These included difficulties in draining and infusing dialysate, fluid overload, gastro-intestinal symptoms, fatigue, malaise, abdominal distension and diffuse abdominal soreness. In none of their five cases was there fever at presentation.

Miscellaneous: Neisseria were occasionally found to cause peritonitis in three centres (Atkins et al, 1981c; Prowant and Nolph, 1981; Vas et al, 1981a). Neisseria are normal residents of the human oropharynx. Peritonitis due to these bacteria is most likely to have been caused by organisms blood-borne from the mouth. Other organisms isolated once by one or two centres included **Alkaligenes** spp, **Bacillus** spp, **Flavobacterium** spp, **Gaffkya** sp, and **Listeria monocytogenes**.

5. The Laboratory Diagnosis of CAPD Peritonitis

If a case of CAPD peritonitis is to be satisfactorily managed, it is clearly desirable that the causative organisms are quickly and correctly identified. Nevertheless, Table P.3 shows that in most centres no organism was isolated in 20 to 40% of episodes. Several of the authors reporting from these centres described such culture negative episodes as "sterile" peritonitis (Atkins et al, 1981b) and implied that at least some were not due to micro-organisms at all. However, the fact that three centres were able to isolate organisms in almost all episodes suggests that their less successful colleagues were using inadequate culture techniques. In this section, the various laboratory diagnostic methods employed are evaluated.

White Cell Count

As described in section 3, a constant feature of CAPD peritonitis is a raised dialysate white cell count. The white cell density in uninfected dialysate is 0-80/mm^3 (Prowant and Nolph, 1981). With the onset of peritonitis, the white cell density rises rapidly to over 300/mm^3 and often much more (Rubin et al, 1980). In most instances, the great majority of white cells in infected dialysate are polymorphonuclear leukocytes. Vas et al (1980) stated that a dialysate polymorph count of 100/mm^3 or more strongly suggested infection. This nice, round figure has since become widely accepted (Moncrief and Popovich, 1981b).

As discussed earlier, the "cloudy bag" is a cardinal feature of CAPD peritonitis, but there are other causes of cloudy dialysate. Slight intraperitoneal bleeding, such as may result from retrograde flow during menstruation is one (Moncrief J W, in Atkins et al, 1981a, p295); lipid and fibrin are, rarely, others (Prowant and Nolph, 1981). Peritoneal eosinophilia of unknown origin has also been reported (Oreopoulos et al, 1981b).

Consequently, the clinical diagnosis of CAPD peritonitis should always be confirmed by a dialysate white cell count, preferably using a haemocytometer (Moncrief and Popovich, 1981b).

The Gram Stain

Instinctively, the bacteriologist will then want to perform a Gram stain, in the hope of seeing the causative organisms. However, this is generally unsuccessful. Rubin et al (1980) found the Gram stain revealed organisms in only 9% of 87 specimens, even when a centrifuged deposit was studied. Vas (1981) reported that organisms were seen on the dialysate Gram stain in 35% of all episodes of CAPD peritonitis. Other authors did not indicate that they found the Gram stain helpful.

Culture

The frequent failure to see organisms on the Gram stain suggests that they are either present in very small numbers, cannot be conventionally stained or do not exist. That the first explanation is likely to be correct in most cases was shown by Rubin et al (1980). They carried out colony counts on ten samples of infected dialysate and found a density of only 0.25 colony forming units/ml or less in half the samples. The organisms isolated in such small numbers were **Staph. epidermidis, P. aeruginosa, Enterobacter agglomerans, Strep. faecalis** and **Candida albicans.** Such a low density of organisms contrasts sharply with, for example, that found in a urinary tract infection where the normal diagnostic threshold is 10^5 organisms/ml of urine.

Further circumstantial evidence that the culture negative episodes were caused by bacteria was provided by Atkins et al (1981b). Comparing 109 episodes of culture positive peritonitis with 45 episodes of culture negative peritonitis, they found that the clinical presentations in the two groups were indistinguishable except for the mean duration of symptoms prior to admission: culture positive - 25 hours, culture negative - 19 hours. The mean dialysate white cell count was very similar in both groups. However, 40% of the culture negative episodes resolved following peritoneal lavage without antibiotics compared with only 5% of the culture positive episodes and the mean duration of symptoms was significantly shorter in the culture negative group. This suggests that many, if not all, the culture negative episodes were caused by less pathogenic or less well-established organisms than those causing the culture positive episodes.

In a search for a more sensitive means of culture, Rubin and his colleagues (1980) tested three methods:-

(1) Inoculation of 5 ml of dialysate into supplemented peptone broth;

(2) Passage of 100 ml of dialysate through a 0.45 μm pore-diameter membrane filter in an anaerobic "glove box". The filter was divided and incubated both aerobically and anaerobically on sheep blood agar;

(3) Addition of 17 ml of dialysate to a plastic cylinder containing a dessicated nutrient agar pad overlain by a 0.45 μm pore-diameter filter. As dialysate was drawn through the filter to rehydrate the nutrient pad, any bacteria present would be trapped on the filter. The filter and pad were then incubated together.

These methods were compared using dialysate from 97 episodes of CAPD peritonitis. Broth culture was positive in 73% of samples, the filter in 81% and the filter-nutrient pad in 61%. The differences were not statistically significant. The authors did not indicate if certain species were more readily isolated by one method than another.

Atkins and his colleagues (1981b) compared several methods. They found that culture of the deposit of 150 ml of centrifuged dialysate yielded organisms in 75 of 100 episodes compared with 63% of 54 episodes when only 15 ml of dialysate was centrifuged (X^2 = 1.9, $p > 0.10$). They then compared 150 ml deposit culture with culture of 100 ml of dialysate in 900 ml of 0.1% soy agar and culture of 0.2 µm pore-diameter filters through which up to one litre of dialysate had been passed. Using samples from only 23 episodes of peritonitis, they concluded that centrifuged deposit culture and large volume broth culture were equally sensitive and both more sensitive than the filtration technique. The number of samples tested was, however, too small for any statistically valid conclusion to be drawn from their results. Overall, despite their efforts, 29% of episodes proved to be culture negative.

Chan et al (1981) did not describe their methods but found that by adding dialysate to thiol enriched broth, they improved their positive culture rate from 31 to 79%. The other centres reporting low culture rates did not describe their culture methods.

Of the three centres reporting successful culture in 96% of cases (Table P.3), only two described their methods. Vas et al (1981a) used the Addichek system (Millipore Inc), designed for checking the sterility of pharmaceutical products. This consisted of a plastic cylinder containing a 0.45 µm pore-diameter filter.

After passing 100 mls of diaylsate through the filter, the cylinder was filled with thioglycollate broth and incubated. Growth thereafter could usually be detected visually. Although this method was very sensitive, they found the filter often became blocked with white cells and fibrin. In such cases they centrifuged the fluid and cultured the deposit. However, they felt that contamination was more likely to occur during centrifugation.

Mergerian (1981) inoculated 5 ml of dialysate into each of the following four liquid media:-

(1) Thioglycollate broth, incubated anaerobically at 37°C;

(2) Glucose broth, incubated aerobically at 37°C;

(3) Two Sabouraud broths, incubated at 37°C and 22°C respectively.

He reported that in only two of 44 episodes were organisms not isolated, but did not indicate the relative usefulness of the different media.

Only tentative conclusions can be drawn from these very limited studies. Where dialysate was filtered or centrifuged and the filter or deposit then transferred to solid media, the culture negative rate was high. Greater success was achieved when the dialysate or its filtrate was cultured in a rich liquid medium, capable of growing both aerobic and anaerobic organisms. None of these studies showed conclusively that the isolation rate was increased by increasing the volume of dialysate processed. However, as the number of organisms present appears often to be small, it would seem sensible to culture the largest volume practicable.

If the culture negative episodes are caused by micro-organisms, what are they? Only Vas et al (1981) - 4/103 episodes - and Moncrief and Popovich (1981) - 1/25 episodes - isolated anaerobes, suggesting that some of the undiagnosed infections in other centres could have been caused by anaerobes. Coagulase-negative staphylococci caused a higher proportion of the infections diagnosed by Vas et al than in other centres, suggesting that infections caused by these organisms may also have been underdiagnosed. However, the proportion of infections caused by coagulase-negative staphylococci in the studies by Mergerian (1981) and Moncrief and Popovich (1981), both of whom reported an isolation rate of 96%, was lower than that of Lameire et al (1981) whose diagnostic rate was only 78%. Consequently, examination of these studies does not specifically incriminate any one organism as the cause of undiagnosed infections.

Atkins et al (1981b) used a wide range of methods in an attempt to isolate fastidious organisms such as mycoplasmas, viruses or lipophilic yeasts. None were found. They also found no evidence that endotoxin caused peritonitis in their patients, a possibility suggested by a Canadian report (Kovanicolas et al, 1977). They concluded that "sterile" peritonitis probably had several causes, with the freshness, temperature and volume of the dialysate sample all being important. Antibiotics or antiseptics in the dialysate might also occasionally be responsible.

Of these authors, only Vas et al (1981) attempted to provide clear guidelines to assist other laboratories in the daily task of culturing dialysate. While their results were impressive, their methods could be criticised on several grounds. The Addichek system was expensive and required expert manipulation. The filter was readily blocked and in such cases another less satisfactory method had to be used. If the sample was taken outside normal laboratory hours, its culture would be delayed unless an emergency on-call technician was available.

6. The Treatment of CAPD Peritonitis

Hospital Admission and Peritoneal Lavage

By 1981, there was general agreement that CAPD peritonitis should be treated as soon as it has been clinically diagnosed (Oreopoulos et al 1981c; Moncrief and Popovich, 1981). It was agreed that to wait for the results of culture would be to risk the transformation of a minor nuisance into a life-threatening illness. A review of the methods of treatment used by different centres shows, however, that in other respects treatment differed markedly from centre to centre. Only two centres (Rubin et al, 1980; Moncrief and Popovich, 1981) did not admit all patients with peritonitis to hospital. Once in hospital, all patients in most centres underwent peritoneal lavage and were given intraperitoneal antibiotics. Peritoneal lavage is a technique whereby dialysate is flushed in and out of the peritoneal cavity at frequent intervals. The aim is to remove "the inflammatory mediators of tissue injury, such as the vasoactive amines as well as debris, fibrin, bacteria and exotoxin" (Atkins et al, 1981c). The duration of lavage varied from centre to centre. Lameire et al (1981) continued until symptoms had disappeared; Chan et al (1981) continued for at least 24 hours; Atkins et al (1981c) for three days. Rubin et al (1980) and Moncrief and Popovich (1981) maintained, however, that lavage was not necessary unless the peritonitis was severe. That lavage might even be counter-productive was shown by a series of **in vitro** experiments carried out by Vas et al (1981b). They found that peripheral blood leukocytes phagocytosed and killed **Escherichia coli** most efficiently in dialysate that was isotonic and at pH 7.4. Fresh dialysate, which is hypertonic and at pH 5.2, significantly inhibited both phagocytosis and intracellular bacterial killing. Bacterial killing was also slowed considerably if the density of bacteria and white cells was decreased. Vas and his colleagues thus argued that frequent peritoneal lavage would prevent natural defence mechanisms from acting effectively. They felt that lavage was beneficial in the early treatment of severe peritonitis because it removed inflammatory products and hence relieved the acute symptoms. They believed that thereafter bacterial killing would be enhanced if the dialysate remained in the peritoneal cavity for long periods. The pH and osmolality of the dialysate would then become more physiological, thereby allowing the phagocytes effectively to function in concert with the antibiotics.

Clinical evidence against the need for lavage came from P. Williams and his colleagues (1981). They studied 24 patients with peritonitis, all treated with the same intraperitoneal antibiotics. Twelve were given peritoneal lavage and twelve continued CAPD normally. They found that all the patients recovered, but culture of the dialysate remained positive for much longer in the lavage group (mean 8.7 days) than in the normal CAPD group (mean 2.4 days). Patients receiving lavage also spent longer in hospital (mean 12.25 days versus 6.7 days).

If lavage was unnecessary, then there was little reason to treat patients with mild peritonitis in hospital. So argued Rubin et al (1980), who treated 49 of 97 episodes of peritonitis at home. In only six of the 49 cases was infection not successfully controlled. Moncrief (quoted in Atkins et al, 1981a, p341) pointed out that patients who knew that peritonitis was always treated in hospital were often reluctant to contact their dialysis centre until symptoms became severe. In his experience, patients who knew they were likely to be treated at home promptly reported the development of cloudy dialysate. This may explain the observation that the patients of Fenton et al (1981) (who treated all peritonitis in hospital) had on average more severe symptoms than those reported by Prowant and Nolph (1981) who treated mildly ill patients at home (see Section 3).

There was thus both experimental and clinical evidence that peritoneal lavage was not a necessary part of the treatment of mild or moderately severe peritonitis; and clinical evidence that such episodes could be satisfactorily treated at home. The high cost of hospital treatment was stressed in two reports. Rubin et al (1980) calculated that the average cost per episode of treating a patient with peritonitis in hospital was $1,600. They found that in-hospital treatment virtually annulled the cost advantage of CAPD compared with haemodialysis. Atkins et al (1981c) found that in-patient treatment ranged from $1,085 for an uncomplicated infection to $6,885 for one caused by antibiotic resistant **Staph. aureus.** Thus, although a reduction in the incidence of peritonitis was rightly seen by all authors as a principal objective, effective home treatment of peritonitis emerges as a means of substantially reducing the disruption and extra costs caused by peritonitis.

The Choice of Antibiotics

Because treatment of CAPD peritonitis is usually started before the causative organism is known, it is sensible to start with antibiotics active against most of the likely bacteria. As discussed in Section 4, the range of organisms is similar in all centres. Nevertheless, the choice of antibiotics for the initial treatment of CAPD peritonitis varied considerably. In North America, the first generation cephalosporin, cephalothin, was generally used. Rubin et al (1980) and Moncrief and Popovich (1981b) added 125 mg/l of cephalothin to every bag of fresh dialysate. Cephalothin is active against most staphylococci and streptococci but inactive against **Strep. faecalis, P. aeruginosa** and many strains of the **Enterobacteriaceae** (Garrod et al, 1981). Consequently, Oreopoulos et al (1981a) combined cephalothin with tobramycin (8 mg/l/bag), and Vas (1981) reported that this combination was active against 98% of bacteria isolated from infected dialysate.

In the United Kingdom, cefuroxime was favoured (Bint et al, 1980). This is a second generation cephalosporin which is less active against Gram positive cocci than cephalothin but more active against some Gram negative bacilli (Garrod et al, 1981). It was used singly by Gokal et al (1980) in a dose of 200 mg/l of dialysate but combined with the antistaphylococcal agent flucloxacillin, also given intraperitoneally, by Chan et al (1981). In Belgium, either gentamicin or cotrimoxazole was the most popular first choice (Lamiere et al, 1981), their dosage or route of administration not being specified. In France, Mion et al (1981) used the aminoglycoside, kanamycin, adding 20 mg/l to each bag.

Only Oreopoulos et al (1981b) explicitly stated that their initial treatment, cephalothin and tobramycin, was based on an analysis of the antibiotic sensitivities of organisms they had isolated from infected dialysate. Very few centres attempted to describe the results of treatment with any given antibiotic. The data of Rubin et al (1980) are ambiguous but suggest that of 49 episodes of peritonitis treated initially at home, only 32 (65%) responded satisfactorily to cephalothin alone. Their data are insufficient to assess the results of treatment in hospital. Moncrief and Popovich (1981) did not detail their results but stated that 85% of episodes responded to three days of intraperitoneal cephalosporin followed by five to seven days of oral cephalosporin. Chan et al (1981) found that an initial combination of flucloxacillin and cefuroxime cured 75% of episodes. It was not possible to determine the success of treatment with any given antibiotic from the data presented by other authors.

Two groups reported that treatment had been complicated by the emergence of antibiotic resistant staphylococci. Chan et al (1981) reported that eight of 21 strains of coagulase-negative staphylococci were resistant to flucloxicillin (their antibiotic of choice) and many other antibiotics. Atkins et al (1981c) found that 16 of 38 isolates of coagulase-negative staphylococci and seven of twelve isolates of **Staph. aureus** were resistant to the following antibiotics: penicillin, methicillin, cephalothin, kanamycin, gentamicin, tobramycin, cotrimoxazole, chloramphenicol, tetracycline and erythromycin. All isolates were, however, sensitive to vancomycin. They reported that antibiotic resistance led to the mean length of hospital admission per episode increasing from 5.6 to 10.7 days when caused by coagulase-negative staphylococci, and from 6.6 to 35.8 days (sic) when caused by **Staph. aureus.**

Catheter Removal

By 1981, criteria for the removal of the intraperitoneal catheter in the event of infection had been published by two centres. Moncrief and Popovich (1981) and Oreopoulos and others (1981b) both recommended removal of the catheter and drainage of the peritoneal cavity when there was failure to respond to peritoneal lavage and appropriate antibiotics. Specific criteria for removal shared by both groups were: fungal or tuberculous peritonitis; peritonitis accompanied by severe catheter tract infection; and peritonitis due to bowel perforation. In the event of fungal peritonitis, Oreopoulos recommended that the catheter could usually be replaced after two or three weeks. In no report was there a comprehensive analysis of the episodes of peritonitis which resulted in catheter removal. Several authors indicated that some patients successfully restarted CAPD a few weeks after catheter removal (Rubin et al. 1980; Oreopoulos et al. 1981c; Moncrief and Popovich, 1981). However, the long term outlook of these patients was not discussed.

Moncrief and Popovich (1981) stated that patients who had had more than three episodes of peritonitis in their first six months of CAPD were generally advised to switch to haemodialysis if practical. Other centres did not make explicit their criteria for discontinuation of CAPD because of peritonitis. However, it would seem inevitable that policies would vary considerably from centre to centre under the influence of a multitude of factors, ranging from the availability of haemodialysis time to the personalities of the renal physicians.

7. Discontinuation of CAPD or Death Due to Peritonitis

The two most serious consequences of CAPD peritonitis are the discontinuation of CAPD and death. By 1981, several reports had been published showing that both outcomes occurred with worrying frequency. Most centres had been using CAPD for only two or three years and therefore many of their patients had been using the technique for only a few months. Nevertheless, over 8% of all patients who had been trained in the pioneering centres had already discontinued CAPD because of peritonitis and at least 26 of the patients covered by the reports had died from peritonitis (Table P.4).

Some centres appeared more successful than others at avoiding discontinuation and death. Mion et al (1981) in France, who reported an extremely low peritonitis rate, discontinued CAPD because of peritonitis in only two of 94 patients compared with seven of 50 discontinued by Heale et al (1981) in Australia ($X^2 = 5.95$, $p < 0.02$). However, the average duration of CAPD per patient in the French report was little more than half that reported by the Australians (Table P.4). The higher rate of discontinuation in the latter centre may simply reflect a longer exposure to the risk of infection.

TABLE P.4

PERMANENT DISCONTINUATION OF CAPD OR DEATH DUE TO PERITONITIS

Report	Number of Patients	Mean Duration of CAPD/ Patient (Months)	Number of Patients Discontinuing CAPD (%)	Deaths Due to Peritonitis
Heale et al (1981)	50	14.0	7 (14%)	1
Williams et al (1980)	315	13.3	30 (9.5%)	12
Rubin et al (1980)	18	10.5	2 (11%)	0
Thompson et al (1981)	54	10.3	7 (13%)	1
Lindholm et al (1981)	31	7.8	1 (3%)	0
Mion et al (1981)	94	7.6	2 (2%)	2
Lameire et al (1981)	99	6.8	7 (7%)	5
Morrison et al (1981)	32	5.9	4 (12%)	0
Gokal and Ward (1981)	325	not available	28 (9%)	≥ 5
Total	1,018		88 (8.6%)	≥ 26

Very little information was available about the major factors contributing to discontinuation of CAPD or death. These could include:-

(1) The general condition of the patient, including his or her age and the nature of any underlying disease;

(2) The nature of the infecting organism(s);

(3) The delay between the onset of infection and the start of treatment;

(4) The type of treatment given;

(5) The centres' policy for removal of the intraperitoneal catheter and temporary or permanent discontinuation of CAPD.

Oreopoulos et al (1981b) reported five patients who had died of peritonitis. One had dementia, one a cerebral infarct, one severe wasting and one developed abscesses secondary to diverticulitis and treatment was withheld because of his general condition. The two episodes of fatal peritonitis in the series described by Fenton et al (1981) were both caused by virulent organisms: **Strep. pneumoniae** and **Strep. agalactiae.** Both were in septic shock on admission to hospital, more than 24 hours after the onset of symptoms. As these organisms are virtually always highly sensitive to the penicillins, it is quite likely these patients would have survived if treated earlier.

No details of the other fatal episodes of peritonitis were given, and thus the possibility that some were due to ineffective treatment cannot be explored. However, it is clear that the antibiotics used by many centres for the initial treatment of peritonitis are inactive against some potentially dangerous bacteria. For example, cephalothin alone would be ineffective against **P. aeruginosa, Enterobacter cloacae.** many strains of **Proteus** spp and **Bacteriodes fragilis.** Both gentamicin (Lameire et al, 1981) and kanamycin (Mion et al, 1981) would leave the patient unprotected against streptococci in particular. As culture and antibiotic sensitivity results are rarely available within 24 hours, in such circumstances effective treatment may be long delayed, with possibly disastrous consequences.

8. **Antibiotic Toxicity**

Most authors giving details of their antibiotic treatment of CAPD peritonitis stated that they used aminoglycosides. Some, such as Mion et al (1981) and Oreopoulos et al (1980) used them to begin treatment. Others used them only when they were specifically indicated (Rubin et al. 1980). All aminoglycosides are normally renally excreted and are potentially ototoxic. Ototoxicity is thus a major hazard of their use in patients in renal failure. Does the manner in which they are used in treating CAPD peritonitis place the patient at risk of ototoxicity?

Intraperitoneal administration appears a logical way of ensuring that the bacteria causing CAPD peritonitis are exposed to lethal concentrations of aminoglycoside, whilst the patient is relatively shielded from its toxic effects. It quickly became the route of choice, with most centres opting for either gentamicin or tobramycin. However, the intraperitoneal dose per litre varied considerably.

Chan et al (1981) used 3.3 to 6.6 mg/l; Moncrief and

Popovich, 5 mg/l; Gokal et al (1980), 8 mg/l; Oreopoulos et al (1981b), 8 mg/l, preceded by a loading dose of 1.7 mg/kg bodyweight; Atkins et al (1981c), 10 mg/l. Oreopoulos et al (1981b) stated that their dosage schedule led to a serum concentration of 6-8 mg/l "which is not otoxic". De Paepe et al (1981) studied three patients treated with intraperitoneal gentamicin at a concentration of 7.5 mg/l of dialysate. They found that serum concentrations reached 3-5 mg/l within five days. Mawer et al (1974) described vestibular toxicity in five patients treated with gentamicin, in three of whom the peak serum concentration did not exceed 8 mg/l. They concluded that there was a high risk of ototoxicity if the product of the trough serum concentration in milligrams per litre and the number of days of treatment exceeded 45. Thus, by their reckoning, ten days of treatment resulting in a persistent serum concentration of gentamicin of 6-8 mg/l would carry a high risk of ototoxicity. Smith et al (1980) compared the nephrotoxicity and ototoxicity of gentamicin and tobramycin in a prospective randomised double-blind study. They found that although tobramycin was significantly less nephrotoxic than gentamicin, both drugs caused ototoxicity in about 10% of patients. Peak serum concentrations of both antibiotics in their patients were below 7 mg/l and trough concentrations only 2.5-3.5 mg/l.

Thus, although no reports of aminoglycoside induced toxicity occurring in CAPD patients had been published by 1981, it was apparent that the intraperitoneal doses commonly used were potentially ototoxic. Toxicity would seem particularly likely to occur in patients receiving several courses of aminoglycosides in succession.

9. **At the conclusion of 1981,** CAPD had emerged as an effective form of dialysis, particularly suitable for treating certain types of patient, and was already being widely used. However, despite important technical improvements, bacterial peritonitis remained the major complication of CAPD, although its incidence varied considerably from centre to centre. Patient error during the dialysis exchange was most often blamed as the source of the infection. It seemed unlikely that peritonitis could be eliminated until technical developments had substantially reduced the risk of contamination during the bag exchange.

Peritonitis was caused by a limited range of bacteria, most of which can be found on the human skin. However, in many centres, causative organisms were not isolated in a large proportion of cases. Inadequate culture methods seemed most often responsible. A cheap, simple and effective culture technique had yet to be designed. Most patients with peritonitis were treated in hospital, an approach that was clearly costly and disruptive. Two centres had, however, shown that some patients could be effectively treated at home.

Antibiotics were generally given intraperitoneally but the choice of antibiotic varied considerably. Several of the antibiotics used to start treatment were inactive against organisms commonly causing peritonitis. Aminoglycosides were used in some centres at doses likely to be ototoxic in some patients. The rates of discontinuation of CAPD and death due to peritonitis also suggested that the treatment used by some centres at least was suboptimal. The ideal of safe, effective, home treatment of peritonitis for most patients had not yet been achieved.

10. CAPD Peritonitis at the Queen Elizabeth Hospital, in 1981

The first patient to use CAPD at the Queen Elizabeth Hospital, Birmingham, was trained early in 1981. By the end of that year, twelve patients had been established on CAPD, a full-time nursing sister had been assigned to their care and a room set aside for their exclusive use. As the hospital's haemodialysis facilities were being fully used and patients in chronic renal failure continued to be referred to the hospital, it seemed likely that the number of patients using CAPD would increase steadily.

My association with the renal unit at the Queen Elizabeth Hospital began at the end of 1981. By then, it was already clear that peritonitis was the main threat to the success of the CAPD service. Ten of the twelve patients on CAPD had already developed peritonitis, including two who had had three episodes. The overall incidence of peritonitis was one episode every 3.3 patient-months. This was similar to that initially reported by the North American centres which had pioneered CAPD (Rubin et al, 1980) but much higher than that reported more recently by experienced centres (C. Williams et al, 1981; Mion et al, 1981).

The high incidence of peritonitis had led to a growing number of requests for the bacteriological examination of dialysate and consequently to an appreciable increase in the workload of the microbiological laboratory. However, there had as yet been no attempt to establish a rational policy for such requests or to assess the effectiveness of the microbiological diagnostic methods in use.

During 1981, CAPD peritonitis was treated in hospital until the infection was felt to be under control. The antibiotic of first choice was cefuroxime, given as an initial intravenous loading dose of 500 mg followed by 160 mg added to each new bag of dialysate for two weeks. This approach was successful in most cases but had two main drawbacks. Firstly, the high incidence of peritonitis meant that hospital beds were often occupied by CAPD patients with peritonitis, thereby disrupting or delaying the investigation and treatment of other patients. Secondly, on several occasions the bacteria causing peritonitis were resistant to cefuroxime. Furthermore, in three patients the infection was not eradicated by the initial course of cefuroxime, although the causative organisms were apparently sensitive to cefuroxime.

RESEARCH AND DEVELOPMENT OBJECTIVES

Our initial assessment (Prologue, Section 10) showed that CAPD peritonitis at the Queen Elizabeth Hospital was comparable in incidence and nature to that occurring in other centres. With a view to reducing its impact upon the patients, the renal unit and the bacteriological service, a research and development programme was sketched out early in 1982. It consisted of four main objectives:-

(1) To establish an effective routine service for the microbiological diagnosis of CAPD peritonitis;

(2) To analyse the antibiotic sensitivities of bacteria causing CAPD peritonitis with a view to finding the most reliable antibiotics for its initial treatment;

(3) To simplify treatment, so that as many patients as possible could be treated at home with the minimum disruption to their routine;

(4) To reduce the incidence of peritonitis.

The following chapters describe our attempts to meet these objectives, placing them in the perspective of work published by other centres since the beginning of 1982.

CHAPTER 1

ESTABLISHMENT OF A SYSTEM FOR THE ROUTINE BACTERIOLOGICAL EXAMINATION OF CAPD DIALYSATE

Summary: After considering the various steps needed to make the microbiological diagnosis of CAPD peritonitis, a more efficient and economical system was developed. Normally, only cloudy dialysate was examined. The renal unit staff injected dialysate effluent into special culture bottles containing concentrated nutrient broth. These could be incubated immediately without intervention by a technician. They were then subcultured onto solid media after 24 hours incubation. A second sample of dialysate was also sent to the laboratory for a white cell count and, after centrifugation, a Gram stain and culture on solid media. The broth culture method proved both sensitive and convenient and the system has now operated smoothly for over three years. Great emphasis is placed on ensuring effective communication between the laboratory and the renal unit.

Introduction

With the advent of CAPD at the Queen Elizabeth Hospital, the hospital microbiology laboratory was faced with increasing numbers of requests for the bacteriological examination of dialysate. During the first year of CAPD, there were no guidelines as to when dialysate should be examined. Samples were often sent not only when symptoms or signs of peritonitis were present but also during treatment and at regular out-patient consultations, irrespective of the patient's condition. Not infrequently, patients presented with peritonitis at night or during the weekend. The duty physician would then ask the on-call bacteriology technician to examine the dialysate as an emergency. Soon, 15% of all out-of-hours bacteriological requests and one third of those made after midnight were for the examination of CAPD dialysate. CAPD peritonitis had thus quickly become a major generator of laboratory work. It was clearly necessary to establish criteria for sending specimens of dialysate and to assess critically the techniques used to process the dialysate in the laboratory. Otherwise, there was every likelihood that this unbudgeted influx of specimens would disrupt other aspects of laboratory work without the needs of the renal physician necessarily being met. We thus considered in turn the various steps leading to the microbiological diagnosis of CAPD peritonitis. Following detailed consultation with the staff of both the renal unit and the laboratory, it was then possible to establish a service that was satisfactory to both parties.

The White Cell Count

As discussed earlier (p 20), it had been well established that the onset of clinical peritonitis was almost always heralded by the development of cloudy dialysate, due to the greatly increased density of inflammatory cells (Moncrief and Popovich, 1981). It was found that dialysate became visibly cloudy when the white cell count exceeded approximately $100/mm^3$. The white cell count of uninfected dialysate is usually less than $50/mm^3$ and that of infected dialysate greater than $300/mm^3$ (Prowant and Nolph, 1981). Consequently, cloudy dialysate is a very good indicator of infection except in those rare cases where the cloudiness has some other cause (p 30). It was thus decided that a white cell count should be performed only when the dialysate was cloudy, enabling the diagnosis of peritonitis to be affirmed and providing a baseline against which the effect of treatment could be measured. Under normal circumstances, a white cell count on clear dialysate was not justified.

The white cell count would be performed on fresh dialysate using a Fuchs-Rosenthal haemocytometer. A differential count of polymorphonuclear leukocytes and other white cells would be made and the count reported as the number of cells per cubic millimeter.

Gram Stain

As discussed earlier (p 31), a Gram stain of cloudy dialysate reveals bacteria in only a minority of cases even when a centrifuged deposit is used. However, it was felt that this cheap and rapidly performed test should be carried out on all specimens, at least until satisfactory culture techniques had been developed. The results of the Gram stain and culture could then be compared. It was also thought that the Gram stain might prove helpful in cases of severe peritonitis, when the density of bacteria might be high, and in the early diagnosis of fungal infection, which requires totally different treatment.

The Gram stain would be performed on a smear of the deposit obtained after centrifuging 20 ml of dialysate in a plastic universal container at 3,000 rpm for 15 minutes.

Dialysate Culture

Studies of the culture of infected dialysate published before 1982 had shown that the presumably infective bacteria were often present in the dialysate in very small numbers (p 31). Consequently, it seemed that the chances of successful culture would be enhanced by processing a relatively large volume of dialysate. During the first year of CAPD at the Queen Elizabeth Hospital, a simple centrifugation method was used. This method led to successful culture in only 12 of the 21 episodes of peritonitis during that period, a rate of positive culture similar to those reported by other centres using centrifugation.

We have already seen (p 33) that in only two adequately described studies were causative organisms isolated in more than 90% of cases. In both, the organisms were cultured in liquid medium. In one, dialysate was passed through a filter and the filter then submerged in broth. In the other, 5 ml of dialysate were added to each of four tubes of liquid medium. It was clear, however, that filtration has several disadvantages. The dialysate cannot be cultured until it has been carefully processed by a skilled technician: this will lead either to delay or extra expense if the samples are taken outside laboratory hours. The filter is readily blocked when the dialysate contains a lot of white cells and fibrin. Special precautions are necessary if anaerobes are to be successfully cultured. Filters are expensive.

To permit the culture of a large volume of dialysate without the need for centrifugation or filtration, the following technique was adopted. Twenty millilitres of nutrient broth prepared at four times the normal culture concentration were added to a standard

100 ml blood culture bottle, and then sterilised. By adding 60 mls (the contents of the largest standard syringe) of dialysate to the bottle, the broth was diluted to the correct concentration. The culture bottle could then be treated exactly like a blood culture bottle. In particular, if the bottle was inoculated outside laboratory hours, it could be incubated immediately in the out-of-hours blood culture incubator. There was thus no need for intervention by laboratory staff until the following day.

A suitable nutrient broth had to have two main characteristics. It had readily to permit the growth of a wide range of aerobic and anaerobic organisms including staphylococci, streptococci, **Enterobacteriaceae, Bacteriodes fragilis** and fungi. It also had to be fully soluble at four times its normal concentration. A broth which appeared to satisfy these requirements was Oxoid no 2.

From 1 March 1982 onwards, dialysate was processed using both liquid culture and culture of a centrifuged deposit. It was soon evident that liquid culture was indeed the more sensitive method. During the first three months, dialysate from 21 episodes of peritonitis was cultured and organisms were isolated from all samples. However, organisms were isolated by liquid culture in 19 of the 21 episodes compared with only 12 of 21 by deposit culture ($X^2 = 4.43$, $p < 0.05$). Table 1.1 shows that the majority of organisms isolated by liquid culture alone were coagulase-negative staphylococci. A **Staph. aureus** and an **Acinetobacter calcoaceticus** were isolated only by deposit culture. In the light of these encouraging results, it was decided to continue to use both methods

TABLE 1.1

METHOD OF CULTURE OF BACTERIA FROM 21 CONSECUTIVE EPISODES OF CAPD PERITONITIS MARCH - MAY 1982

	Method of Culture		
Organism	Both	Liquid Culture Only	Deposit Culture Only
Coagulase-negative staphylococci	6	6	0
Staphylococcus aureus	0	0	1
Streptococcus spp	1	1	0
Gram negative bacilli	3	2	1
Total	10	9	2

routinely. The results of a comparison of the two methods over two years are given in the following chapter.

As discussed above, it had been judged that a white cell count on macroscopically clear dialysate could not normally be justified. To determine whether there was any value in **culturing** clear dialysate, we cultured a series of 88 specimens taken at random over a two month period from patients who, clinically, did not have peritonitis, and in which the white cell count was less than $100/mm^3$. On only seven of the 88 occasions (8%) was an organism isolated (coagulase-negative staphylococci (3), diphtheriods (2), **Serratia marcescens** (1), and **Strep. faecalis** (1)). On none of these occasions did peritonitis due to the organism isolated subsequently develop. These results indicated that the culture of clear dialysate in asymptomatic patients would rarely if ever hasten the diagnosis of peritonitis. The culture of clear fluid could thus not normally be justified. A fuller discussion of the significance of the organisms isolated from clear dialysate appears on page 67.

The results of this assessment of the various facets of the bacteriological examination of dialysate were discussed with the staff of the renal unit and the laboratory and agreement reached. The arguments against the need for an out-of-hours service are set out in Appendix 1. Appendix 2 is a summary of the instructions issued to renal unit and laboratory staff at the Queen Elizabeth Hospital. Appendix 3 is a summary of similar proposals adopted by staff at the Centre D'Hemodialyse des Hospices Civils de Lyon.

Discussion

This bacteriological policy has now been in use for over three years. As well as being effective microbiologically, it has also proved extremely satisfactory economically and ergonomically. The culture bottles are prepared in batches in the laboratory media room and stocks maintained in the CAPD room in the renal unit. Because the analysis of clear fluid has ceased, the number of specimens received has been kept within manageable limits, despite the rapid increase in the number of patients treated: 12 in 1981, 108 in 1984. The elimination of out-of-hours requests has also meant considerable savings. Once the culture bottles reach the laboratory, they are treated exactly like blood cultures and consequently can be processed by all levels of laboratory staff without special training. A satisfactory system has thus been laid down. A key element in its success, however, has been, and remains, the close contact that exists between the renal unit and the laboratory. This ensures that results are transmitted to the renal unit staff as soon as they are available, allowing therapeutic decisions to be made without undue delay.

CHAPTER 2

A COMPARATIVE STUDY OF TWO METHODS OF CULTURE OF CAPD DIALYSATE

Summary: Two methods of culture of dialysate effluent were compared using samples from 148 episodes of CAPD peritonitis. Addition of 60 mls of dialysate to concentrated nutrient broth yielded growth in 89% of cases; culture on solid media of a centrifuged deposit from 20 mls of dialysate in only 65%; and the two methods combined in 95%. Coagulase-negative staphylococci and streptococci were isolated much more readily by broth culture. Several strictly aerobic Gram-negative bacilli were isolated only on solid media. These results show that the microbiological diagnosis of most cases of CAPD peritonitis can be made without recourse to expensive or complex techniques.

Introduction

In this chapter, I present the results of a two year prospective study comparing the two methods of dialysate culture routinely used at the Queen Elizabeth Hospital: culture of 60 mls of dialysate in nutrient broth, and culture on solid media of a centrifuged deposit of 20 mls of dialysate.

Patients and Methods

All patients presenting with CAPD peritonitis at the renal unit of the Queen Elizabeth Hospital between 1 March 1982 and 29 February 1984 were included in the study. Patients had been instructed to attend the hospital renal unit if their dialysis effluent became cloudy or if they developed abdominal pain, nausea, vomiting or fever. A diagnosis of infective peritonitis was made if the polymorphonuclear leukocyte count in the dialysate exceeded $100/mm^3$.

After the patient's clinical condition had been assessed by the duty doctor, 80 mls of dialysis effluent were removed from the dialysate bag by the injection port (previously cleaned with an alcohol soaked swab) using a sterile syringe and needle. Using a fresh sterile needle, 60 mls were injected into a 100 ml blood culture bottle containing 20 ml of sterile nutrient broth (Oxoid No 2) at four times normal culture concentration. The remaining 20 ml were placed in a sterile plastic universal container. During normal laboratory working hours, all samples were sent directly to the laboratory. At other times, the dialysate culture bottle was kept in the out-of-hours incubator at 37°C and the universal container in a refrigerator at 4°C until the laboratory opened.

In the laboratory, the fluid in the universal container was gently shaken and several drops removed for a cell count in a Fuchs-Rosenthal haemocytometer. The remainder was centrifuged at 3,000 rpm for 15 minutes. All but a drop of the supernatant was discarded and the deposit resuspended. A small portion was used to make a Gram smear and the remainder inoculated onto blood and CLED agar for aerobic incubation and blood agar for anaerobic incubation. The culture bottle was incubated aerobically. Subculture onto solid media for both aerobic and anaerobic incubation was performed routinely after 24 hours incubation and at any time during the next eight days if growth was seen. Isolates were identified using conventional techniques.

Results

There were 155 episodes of CAPD peritonitis during the study period. In seven, only one of the two methods of culture was used. The study is therefore based on 148 episodes.

In 87 episodes (59%), bacteria were isolated by both methods. In 82 of these, both methods yielded the same organism (one species in 80 and two in two); in two, each method yielded a different organism; and in three, bottle culture yielded two organisms and deposit culture only one. In 44 episodes (30%), isolation was by bottle culture only (one organism in 43 episodes and two in one). In nine episodes (6%), isolation was by deposit culture alone. In eight episodes (5%), no organism was isolated. Thus, bottle culture led to the isolation of bacteria in 131 episodes (89%), plate culture in 96 (65%) and the two methods combined in 140 (95%).

The method or methods by which each strain was isolated are shown in the Table. This shows that coagulase-negative staphylococci and streptococci were isolated much more readily by bottle culture than by deposit culture. **Staph. aureus, Pseudomonas** spp and **Acinetobacter** spp were isolated with equal facility by both methods. However, an **Agrobacterium** sp (yellow group) and two unidentified aerobic Gram negative bacilli were only isolated by deposit culture, the former repeatedly. On the two occasions that anaerobes were isolated, they were isolated by bottle culture only.

TABLE 2.1

METHOD OF CULTURE OF 148 BACTERIAL ISOLATES FROM DIALYSATE IN 140 EPISODES OF CAPD PERITONITIS

	Method of Isolation		
	Both	Bottle Only	Plate Only
Coagulase-negative staphylococci	46	26	3
S. aureus	10	0	1
Streptococcus spp	5	12	0
Diphtheriods	1	4	2
Acinetobacter spp	4	1	1
Enterobacteriaceae	13	5	1
Pseudomonas spp	7	0	0
Agrobacterium sp	0	0	1
Bacteroides spp	0	2	0
Unidentified aerobic Gram negative bacilli	0	0	2
Yeast	1	0	0
Total	87	50	11

Culture and the Gram Stain

Organisms were seen on Gram stain of the deposit in 39 episodes (27%). In coagulase-negative staphylococcal peritonitis, the Gram stain was positive significantly more often when the organism was isolated by both methods (17 of 45 episodes) than when it was isolated by bottle culture alone (3 of 26 episodes) (X^2 = 5.58, $p < 0.02$). This suggests that liquid culture was the more sensitive method for isolating organisms present in small concentrations.

Culture and the White Cell Count

There was no correlation between the dialysate white cell count and the likelihood of isolation of bacteria by both methods or by either method alone. For example, the mean dialysate white cell count in the 45 episodes where coagulase-negative staphylococci were isolated by both methods was 2,500/mm^3 (SD$\pm$2,700/mm^3) compared with 2,400/mm^3 (SD$\pm$3,400/mm^3) in the 26 episodes where coagulase-negative staphylococci were isolated by liquid culture alone.

Culture and the Response to Treatment

The clinical severity of the peritonitis had no bearing on whether organisms were subsequently isolated by both methods or by one method alone. Gram positive organisms were treated with intraperitoneal vancomycin and Gram negative organisms generally with an aminoglycoside, also intraperitoneally (see chapters 5 and 6). The response to treatment was equally satisfactory in cases where organisms were isolated by both methods and in those where they were isolated by liquid culture alone.

Culture Negative Cases

In five of the eight episodes where there was a raised dialysate white cell count but negative culture, the patient was asymptomatic. Two of the five patients had had recent culture positive peritonitis and had stopped taking antibiotics two and six days before the sample was taken; a third had received intramuscular cefamandole until three days before; one had stopped CAPD for 48 hours before the sample was taken and the dialysate may thus have been unusually concentrated, thereby giving a misleading high white cell count; one was seen on a Saturday and samples were not incubated until two days later. A sixth patient with symptomatic culture negative peritonitis was seen on Christmas Day, again suggesting the possibility of delayed culture. The seventh patient who had severe symptoms of peritonitis had received dental treatment two days before. This points to a streptococcal infection (Vas, 1981), possibly due to a vitamin B_6 deficient strain. The eighth patient also had symptomatic peritonitis. Although intracellular Gram positive cocci were seen on the deposit Gram stain, culture was negative.

All eight patients responded rapidly to intraperitoneal vancomycin and gentamicin.

Discussion

This study showed clearly that liquid culture is a more sensitive method than deposit culture for the isolation of bacteria from infected dialysate. Our liquid culture method led to the isolation of organisms in 89% of cases compared with only 65% by deposit culture. This difference was largely due to the more frequent isolation by liquid culture of coagulase-negative staphylococci and streptococci. Liquid culture also led to the only two isolations of anaerobes. There was evidence that, in part, this superiority lay in the greater ability of liquid culture to permit growth of organisms present in very small numbers: if coagulase-negative staphylococci were isolated by liquid culture alone, the initial Gram stain was significantly less likely to have been positive than if they were isolated by both methods.

The earlier study of the culture of clear dialysate (p 57) showed that organisms can sometimes be isolated from dialysate in the absence of peritonitis. Some of these isolates could have been the result of contamination during sampling or processing. In this respect, liquid culture would appear less vulnerable than deposit culture, as the former requires less manipulation prior to incubation. Alternatively, the isolates could have represented non-pathogenic organisms present in the dialysate during sampling. Slingeneyer and others (1981) studied the use of bacterial filters fitted to the administration tubing with the aim of preventing micro-organisms passing from the dialysate bag or the bag connector to the peritoneal cavity. They cultured 114 filters each of which had been used for between 40 and 60 dialysate exchanges. Organisms were cultured from the bag side only in 26 of the 114 filters, the most common isolates being staphylococci, **Bacillus** spp and yeasts. Their results indicate that organisms find their way into the dialysate relatively frequently but cause peritonitis in only a minority of occasions, even when a filter is not used. Presumably, the organisms are eliminated by the peritoneal cavity's natural defences. It is thus possible that such non-pathogenic organisms may occasionally be isolated from the dialysate of patients **with** peritonitis, whilst the true cause escapes detection. The more sensitive the method of culture, the more frequent are such false positive isolates likely to be. The present study suggests, however, that the organisms isolated by liquid culture alone had the same clinical significance as those isolated by both methods. The clinical features, dialysate white cell count and response to treatment of episodes associated with coagulase-negative staphylococci were similar, irrespective of whether the organisms were isolated by both methods or by liquid culture alone. It thus seems certain that the great majority of organisms isolated by liquid culture alone were genuine pathogens.

Use of the two methods in parallel led to the isolation of organisms in 95% of episodes. The nine isolates which were only cultured from the deposit included three strictly aerobic bacteria. Of these, an **Agrobacterium** sp was repeatedly grown only from the deposit. This suggests that the bottle was insufficiently oxygenated to permit the growth of some fastidious aerobes. Rather than attempting to provide satisfactory conditions for the isolation of all types of bacteria in one medium, greater success might be had if two different liquid media are used. Trials are at present underway in Les Hospices Civils de Lyon using brain heart infusion broth for aerobes and Schaedler broth for anaerobes. Fifty millilitres of cloudy dialysate are injected into each of the two culture bottles, each containing 50 ml of broth at twice normal culture concentration. Should these trials prove successful, deposit culture will become superfluous and the processing of dialysate further simplified.

In only two of the 148 episodes did it seem likely that more complex techniques would have improved the chances of isolating bacteria. One of the eight culture negative cases developed shortly after dental treatment. A viridans streptococcus would thus be the most likely causative organism (p 28) and a pyridoxine containing medium might therefore have revealed a vitamin B_6 deficient strain. In another culture negative case, intracellular organisms were seen. Here, disruption of leukocytes prior to culture might have been helpful. In the other culture negative cases, however, it appeared more likely that antibiotics in the dialysate or delayed culture were to blame.

No major advances in the microbiological examination of dialysate have been published since the start of this study. Knight and others (1982) inoculated 2-3 mls of dialysate into a bottle containing thioglycollate broth under 5% CO_2 and reported a positive culture in 42 of 50 episodes. The Gram stain was positive in only eight episodes. Beardsworth and others (1983) used similar methods and reported a positive culture in 90% of 130 episodes. The Gram stain was positive in 30%. Fenton (1982) described a pour-plate method in which 1 ml of dialysate was mixed with 10 mls of molten nutrient agar and poured into a sterile Petri dish. After the agar had set at room temperature, the plate was incubated for 72 hours at 37°C in air plus CO_2. Organisms were thus isolated in 11 of 14 episodes of peritonitis. However, because the number of episodes considered was so small, the method could not properly be assessed. The method also had two practical disadvantages: the volume of dialysate may be insufficient if few organisms are present; and the medium must be inoculated by skilled laboratory staff, making the method unsuitable for use outside normal laboratory hours.

Filtration continued to be widely used. Both Vas (1983) and Prowant and Nolph (1982) reported that filtration led to the successful isolation of organisms in nearly all episodes. Neither, however, offered a detailed analysis of their results. However, Gokal and others (1982) reported that their filtration method yielded organisms in only 80% of episodes. The expense and inconvenience of filtration, previously discussed (p 54), were generally glossed over by its advocates.

It is thus clear that isolates of organisms in at least 80% of episodes should be readily attainable by all laboratories. Several recent reports indicate, however, that many laboratories continue to fall short of this target. In a survey of 41 dialysis units using CAPD in the United Kingdom, only one half reported they could culture the infecting organism in at least 70% of episodes (Gokal and Marsh, 1984). Only one in five claimed positive cultures in at least 90% of episodes. Whilst the majority of laboratories used methods involving centrifugation, filtration or liquid culture, 25% merely cultured uncentrifuged dialysate using routine laboratory techniques. More recently, Gray and others (1985) in London, using culture of a centrifuged deposit, isolated bacteria in only 48% of cases; Read and others (1985) in Leeds isolated organisms in 60% of cases but did not describe their methods of culture. Poor results were not confined to this side of the Atlantic. Rubin and others (1983) in Missouri also reported that 40% of their episodes were culture negative. They used two methods of culture: 0.5-1 ml of dialysate was inoculated into thioglycollate broth and 0.01 ml of dialysate was streaked onto blood agar plates. Three years earlier, the same principal author had been unable to detect more than 25 organisms/100 ml of dialysate in many episodes of peritonitis (Rubin et al, 1980). Thus, by his own reckoning, the culture methods subsequently used by his collaborators would often have little chance of success.

Most recently, Vas and others (1985) have described further refinements in their methods. They appear to have abandoned filtration in favour of centrifugation; they use resins or washing by repeated centrifugation to remove antibiotics present in the dialysate; and they use the Bactec system to detect bacterial growth early. However, their results do not suggest that these modifications offer any advantage except in the case of the patient already on treatment. Their paper closes with the following sentence: "Although the cost of the above-described methods is considerable, one has to weigh the cost of laboratory diagnosis against the possibility of unnecessary therapy and prolonged hospitalisation." The present study has shown that high laboratory costs can be avoided without endangering the quality of the service.

CHAPTER 3

THE ORGANISMS CAUSING CAPD PERITONITIS AND THEIR ANTIBIOTIC SENSITIVITIES

1. The Coagulase-Negative Staphylococci*

Summary: Forty-three strains of coagulase-negative staphylococci were obtained from dialysis effluent during 41 episodes of CAPD peritonitis. Eighty per cent of these were found to be **Staph. epidermidis** but several other species also occurred. A recurrent infection lasting 15 weeks was caused by **Staph. haemolyticus.** Multiple antibiotic resistance was found to be common. Of 13 antibiotics tested, only vancomycin was active against all strains although most strains were also sensitive to rifampicin, netilmicin and cefamandole. Vancomycin was therefore selected as the most suitable antibiotic for the initial treatment of CAPD peritonitis caused by coagulase-negative staphylococci.

Introduction

Even with efficient methods of culture, the identification of the organisms causing CAPD peritonitis and their antibiotic sensitivities will not be known for at least 24 hours after the patient is first seen. Treatment, however, should normally be begun without delay to bring the infection quickly under control.

* Much of the data in this chapter was included in a paper published in the Journal of Antimicrobial Chemotherapy. See Appendix 4.

Consequently, the initial treatment should include antibiotics active against most if not all the likely causative organisms. This is particularly vital if it is hoped to treat most patients at home. Frequent failure of the initial treatment would render such a policy unworkable. We therefore felt it was essential to determine the antibiotics most likely to control the infection from the outset. We aimed to do this by studying the antibiotic sensitivities of à large number of isolates from the infected dialysate of CAPD patients at the Queen Elizabeth Hospital.

As we saw earlier (p 23), virtually all CAPD centres have found that coagulase-negative staphylococci are the most common cause of CAPD peritonitis. Two reports also showed that these organisms could often be resistant to many antibiotics (Chan et al, 1981; Atkins et al, 1981c). We quickly found that the situation was similar at the Queen Elizabeth Hospital. Twelve of the 21 episodes seen in early 1982 were caused by coagulase-negative staphylococci. These included three of the four episodes which did not respond to cefuroxime, the antibiotic of choice at that time. Each of the three strains was reported as sensitive to cefuroxime but resistant to flucloxacillin and several other antibiotics. However, staphylococci that are resistant to flucloxacillin consistently show reduced sensitivity to the cephalosporins (Lowy and Hammer, 1983). It thus seemed possible that the antibiotic content of the disc used to test for cefuroxime sensitivity was too high to detect reduced sensitivity and that the result of the cefuroxime test could thus be misleadingly optimistic.

It was therefore clear that a detailed study of our isolates of coagulase-negative staphylococci was required due both to the frequency with which they caused peritonitis and to their uncertain sensitivity to antibiotics.

As discussed earlier, all the authors of reports of CAPD peritonitis published before 1982 had described their isolates of coagulase-negative staphylococci as **Staph. epidermidis.** They did not indicate how such isolates had been identified and it must therefore be assumed that they had done no more than confirm that the isolates were staphlococci which did not produce coagulase. It has for long been known that the coagulase-negative staphylococci are a heterogenous group of organisms (Baird-Parker, 1965). However, it was not until 1975 that a manageable classification was proposed (Kloos and Schleifer, 1975). This recognised nine distinct species based on an extensive series of biochemical tests. The species **Staph. epidermidis** was retained but its definition became much more precise. With the acceptance of this classification by the International Journal of Systematic Bacteriology (Schleifer and Kloos, 1975), it henceforth became strictly incorrect to describe all coagulase-negative staphylococci as **Staph. epidermidis** without recourse to further tests. However, because such tests are expensive and time-consuming and the results generally have little if any clinical relevance, the old ways have persisted.

More recently, a rapid micromethod based on the Kloos and Schleifer classification has been developed (Brun et al, 1978). This permits the identification of coagulase-negative staphylococci within 24 hours and has been available in commercialised form for several years. Precise identification of coagulase-negative staphylococci is now possible in all routine microbiological laboratories. A further, as yet imperfect, means of differentiating coagulase-negative staphylococci for epidemiological purposes is phage typing (de Saxe et al, 1981).

As coagulase-negative staphylococci causing CAPD peritonitis had not been studied in any detail before, it seemed useful not only to test their antibiotic sensitivities but also to characterise them as precisely as possible. I thus collected all coagulase-negative staphylococci isolated from the infected dialysate of CAPD patients during the twelve months from 1 May 1982.

Materials and Methods

Initial Isolation and Identification: Dialysate from patients with peritonitis was sampled and processed as previously described (p 60). All isolates of Gram positive cocci resembling staphylococci were purified on Columbia agar base (Oxoid Ltd) by twice plating out from a single colony. Isolates were subjected to the following primary identification tests: catalase, coagulase and oxidation or fermentation of glucose (Hugh and Leifson, 1953). All catalase-positive, coagulase-negative, fermentative isolates were then characterised further.

API Staphylococcus identification galleries (API, Montalieu, Vercieu, France) were used according to the manufacturer's instructions. Tests included in the galleries were the fermentation of glucose, fructose, mannose, maltose, lactose, trehalose, mannitol, xylitol, melibiose, raffinose, xylose, saccharose, amethyl glucoside and N-acetyl-glucosamine; the reduction of nitrate to nitrite; the production of acetyl-methyl-carbinol (V-P test); and the production of alkaline phosphatase, arginine hydrolase and urease. On the basis of the results each isolate was assigned a numerical profile which could then be used to identify the isolate from an index provided by the manufacturer and based on the classification of Kloos and Schleifer (1975).

Biotyping using conventional methods and phage-typing (de Saxe et al, 1981) were carried out by the Central Public Health Laboratory (CPHL), Colindale, London. The tests used were the fermentation of fructose, maltose, lactose, trehalose, mannitol, xylitol, xylose, arabinose, ribose and sucrose; the reduction of nitrate to nitrite; and the production of acetion and alkaline phosphatase. Each isolate was then assigned a biotype according to a modification of the Baird-Parker classification which could then be converted to the Kloos and Schleifer classification (Marples, 1981; Marples and Richardson, 1982).

Antibiotic Sensitivity Testing: Thirteen antibiotics with known anti-staphylococcal activity were tested. The minimum inhibitory concentration (MIC) of each antibiotic for each isolate was found by a standard agar plate dilution method (Waterworth, 1978) with Iso-Sensitest agar (Oxoid Ltd). Control strains of coagulase-negative staphylococci were provided by the Antibiotic Research Laboratory, Dudley Road Hospital, Birmingham and were included on each plate. All MICs were determined after 24 hours incubation except for flucloxacillin, cefuroxime and cefamandole where the determination was made at 48 hours.

A short antibiogram was obtained for each isolate using five antibiotics (gentamicin, erythromycin, clindamycin, flucloxacillin and fusidic acid) to each of which resistance was common and apparently independent. The production of β-lactamase was detected by the method of Park, Lopez and Cook (1978).

Results

A total of 61 isolates of coagulase-negative staphylococci were obtained from 52 specimens of dialysis effluent during the period 1 May 1982 to 30 April 1983. These specimens were collected during 41 episodes of acute peritonitis in 25 patients. A coagulase-negative staphylococcus was twice cultured concurrently with an acinetobacter, once with a **Staph. aureus** and once with a β-haemolytic streptococcus. On seven occasions, two or three colonial types of coagulase-negative staphylococci were obtained from a single specimen. On five of these occasions futher characterisation showed that they were all colonial variants of the same strain, but on two occasions the isolates had different biotypes and antibiograms.

Identification: After considering the source, biotype, phage type and antibiotic sensitivity of each of the 61 isolates, we were able to distinguish only 43 strains. These are classified according to species in Table 3.1 which shows that most were **Staph. epidermidis.** There was close agreement between API and CPHL biotyping as to which strains were **Staph. epidermidis** but several of the other strains were speciated differently by the two methods.

The same strain was isolated more than once from each of nine patients. In five, all the isolates were cultured during the

TABLE 3.1

SPECIATION OF 43 DISTINCT STRAINS OF COAGULASE NEGATIVE STAPHYLOCOCCI FROM PATIENTS WITH CAPD PERITONITIS

	Method of Biotyping	
Organism	API	Conventional*
Staph. epidermidis	36	34
Staph. haemolyticus	2	2
Staph. warneri	1	2
Staph. cohnii	1	1
Staph. capitis	1	0
Staph. simulans	0	2
Staph. hominis	1	2
Untypeable	1	0

* Tests carried out by Central Public Health Laboratory, Colindale

initial course of antibiotics and were not re-isolated thereafter. In three, the same strain was re-isolated between one and three weeks after the first course of treatment but did not recur after the second course. In one patient the same strain of **Staph. haemolyticus** was isolated from the dialysate on four different occasions over a period of 15 weeks. On each of these occasions the patient had peritonitis and no other organism was isolated.

During the 12 months of the study, four patients had two separate episodes of peritonitis caused by different strains of coagulase-negative staphylococci, three patients had three and two had four.

Phage Typing: Only 26 of the 59 isolates tested showed lysis by one or more phages and lysis was often weak. On two occasions, phage typing clearly differentiated isolates from the same patient which had identical biotypes and antibiograms. Phage typing also sometimes confirmed that isolates cultured on different occasions from the same patient were identical.

MIC_{50} and MIC_{90}: All but six of the 43 distinct strains produced β-lactamase. The MICs of each of the 13 antibiotics for 50% and 90% of the strains are shows in Table 3.2. Also included in the Table are the antibiotic concentrations which can be readily but safely achieved in dialysis fluid and blood. Only six of the 13 antibiotics - vancomycin, rifampicin, netilmicin, cefamandole, fusidic acid and clindamycin achieved an adequately low MIC_{90}. All strains were sensitive to 1 or 2 mg/l of vancomycin and only one strain was resistant to rifampicin. All but two strains were sensitive to netilmicin and cefamandole at 2 and 4 mg/l, respectively, but the MICs of both these antibiotics varied between

TABLE 3.2

MIC_{50} AND MIC_{90} OF 13 ANTIBIOTICS FOR STRAINS OF COAGULASE NEGATIVE STAPHYLOCOCCI FROM PATIENTS WITH CAPD PERITONITIS COMPARED WITH ACHIEVABLE DIALYSATE AND BLOOD LEVELS

	No of Strains Tested	MIC_{50} (mg/l)	MIC_{90} (mg/l)	Dialysate* (mg/l)	Blood† (mg/l)
Vancomycin	41	2	2	15	20
Rifampicin	41	0.004	0.008	-	5‡
Netilmicin	41	0.125	1	6	4
Cefamandole	39	1	4	30	10
Fusidic Acid	41	0.125	2	25	20
Clindamycin	42	0.06	0.125	25	5
Flucloxacillin	43	2	>32	50	10
Cephradine	35	16	32	-	10‡
Cefuroxime	35	16	>32	30	10
Erythromycin	42	0.125	>32	-	1.5‡
Gentamicin	41	0.125	16	4	4
Tobramycin	35	0.125	>16	4	4
Trimethoprim	35	>16	>16	-	3‡

* Approximate mean inter-dose level following standard intra-peritoneal dose (Oreopoulos et al, 1981b)

† Approximate mean inter-dose level following standard intravenous dose (or oral dose where marked) suitable for patient with severe renal impairment (Garrod et al, 1981)

‡ Given orally

strains by a factor of up to 64 suggesting that strains with greater resistance might readily emerge. There were three strains resistant to clindamycin (all > 32 mg/l) and four to fusidic acid (> 8 mg/l).

We concluded that vancomycin appeared to have the most consistent activity of all the antibiotics tested. Rifampicin, netilmicin and cefamandole also seemed worthy of further consideration for clinical use.

Antibiograms: Sixteen of the 61 isolates tested were sensitive to all five antibiotics but each of the other 45 isolates was resistant to between one and four. Table 3.3 shows the percentage of strains which were resistant to each of the five antibiotics compared with those from seven other recent studies of coagulase-negative staphylococci isolated from a variety of clinical specimens.

There were 14 different patterns of resistance to the five antibiotics among our isolates, several patterns being unique to isolates from a single patient. On all but one occasion, isolates with identical phage types also had identical antibiograms. Conversely, only twice did an isolate have a different phage type but the same antibiogram. Thus, phage typing and the antibiogram had similar usefulness.

Discussion

Only about 25% of the coagulase-negative staphylococci found on normal human skin are **Staph. epidermidis, sensu stricto** (Kloos and Schleifer, 1975). In contrast, studies of clinical isolates of

TABLE 3.3

PERCENTAGE OF ISOLATES OF COAGULASE NEGATIVE STAPHYLOCOCCI RESISTANT TO FIVE ANTIOBIOTICS IN VARIOUS STUDIES

	Antibiotic				
Authors	Gentamicin	Erythromycin	Clindamycin	Methicillin	Fusidic Acid
CAPD Peritonitis Isolates (n = 43)	40	42	12	35	9
Brun et al (1981) (n = 109)	15	35	28	34	-
Richardson and Marples (1982) (n = 532)	27	31	-	37	25
Marsik and Brake (1982) (n = 203)	8	41	36	66	-
Smith et al (1982) (n = 191)	24	43	36	39	-
Gemmell and Dawson (1982) (n = 100)	0	-	0	0	0
Price and Flournoy (1982) (n = 42)	38	50	52	55	-
Davies and Dyas (1985) (n = 200)	30	36	-	21	-

coagulase-negative staphylococci show that from 63 to 81% are **Staph. epidermidis** (Marsik and Brake, 1982; Gemmell and Dawson, 1982; Sewell et al, 1982) whilst as many as 93% of clinically significant coagulase-negative staphylococcal infections may be caused by **Staph. epidermidis** (Sewell et al, 1982). The present study of 43 distinct strains of coagulase-negative staphylococci, all of which were thought to be clinically significant, showed that about 80% were **Staph. epidermidis.** Thus, the apparently greater pathogenicity of **Staph. epidermidis** compared with other coagulase-negative staphylococci includes a greater propensity to cause CAPD peritonitis. Nevertheless, the infection can also be caused by other coagulase-negative staphylococci. Most notably, **Staph. haemolyticus** was responsible for a recurrent infection lasting 15 weeks.

A beginning has been made in elucidating the mechanisms of pathogenicity of **Staph. epidermidis.** It causes infection almost exclusively following colonisation of implanted plastic materials (Lowy and Hammer, 1983). As catheters, artificial joints and valves and other prosthetic devices have become more and more widely used, so have the opportunities afforded to **Staph. epidermidis** increased. Electromicrographic studies have shown that **Staph. epidermidis** can adhere to and form microcolonies on the surface of synthetic polymers (Peters and Pulverer, 1984). Growth often begins on areas of surface irregularity. The microcolonies secrete extracellular slime which ultimately covers the bacteria completely. This slime, which is thought to be a glycoconjugate complex may have several important functions. It may allow the organisms to adhere firmly to plastic and it may act as a barrier against antibiotics (Peters and Pulverer, 1984). Most recently it has also been shown that the slime can interfere with the immune system (Gray et al, 1984). The lymphoproliferative response of peripheral mono-nuclear cells was shown to be markedly inhibited by the slime. It is not yet clear, however, whether or not the pathogenicity of coagulase-negative staphylococci depends entirely on the production of slime.

Biotyping was found to be helpful in determining which isolates represented persisting and which fresh infection. As other authors have shown, the API Staph. system gave results which correlated well with those of conventional methods, yielding numerical profiles which could be readily compared (Marples and Richardson, 1982; Gemmell and Dawson, 1982; Ellner and Myrick, 1982). Further differentiation of some strains was made possible by phage typing or antibiotic sensitivity testing, but both approaches had disadvantages. The phage-typing system could type only 50% of isolates and extensive antibiotic sensitivity testing is too expensive and laborious for routine, clinical use. The short antibiogram, on the other hand, proved capable of differentiating some strains, as well as providing clinically useful information.

Antibiotic Sensitivities: Resistance to flucloxacillin, cefuroxime, cephradine, gentamicin, tobramycin, trimethoprim and erythromycin was sufficiently frequent among our isolates of coagulase-negative staphylococci to make these agents unsuitable for routine use. Although apparently not universal, resistance to these and other antibiotics is widespread (Table 3.3) and may be increasing. Richards and Marples (1982) have noted that the proportion of gentamicin-resistant strains of coagulase-negative staphylococci has risen from 7% in 1976-77 to 33% in 1980.

Cefamandole and netilmicin were both notably more active than the other cephalosporins and aminoglycosides we tested, a feature also noted by Smith and others (1982). However, we found their MICs varied greatly from strain to strain, suggesting that a progressive decrease in the sensitivity of coagulase-negative staphylococci to both antibiotics might occur if they were used extensively. The activity of cefamandole against coagulase-negative staphylococci has been shown to be virtually identical to that of cephalothin, the antibiotic most frequently used for treating CAPD peritonitis caused by coagulase-negative staphylococci in North America (Price and Flournoy, 1982). However, several studies have shown that the activity of both these antibiotics is markedly reduced against the frequently encountered methicillin-resistant strains (Archer, 1978; Laverdiere et al, 1978; John and McNeill, 1980). Such reduced sensitivity can be most readily revealed using a heavy inoculum of organisms with incubation at 30°C for 48 hours (John and McNeill, 1980). These authors found that the mean MIC of cefamandole against 28 strains of methicillin-sensitive coagulase-negative staphylococci was 1 mg/l with a maximum value of 8 mg/l. In contrast, its mean MIC against 54 methicillin resistant strains was 31 mg/l with some strains being resistant to greater than 250 mg/l. They also found that whilst cefuroxime was active against all methicillin-sensitive strains, its mean MIC against methicillin-resistant strains was greater than 1,000 mg/l. These results reinforce our conclusion that cefuroxime is totally unsuitable for treating methicillin-resistant coagulase-negative staphylococci. As these strains accounted for more than one-third of our isolates, cefuroxime clearly had no place in the initial, blind treatment of such infections. Likewise, they confirm our impression that the relative resistance of some strains to cefamandole and cephalothin meant that these antibiotics were less than ideal. Despite the excellent activity of rifampicin against all but one strain, we felt that its special role in the treatment of tuberculosis precluded its routine use in CAPD peritonitis.

All the isolates tested in the present study were sensitive to vancomycin. In most published studies of the sensitivity to vancomycin of coagulase-negative staphylococci, all isolates tested have been sensitive to 4 mg/l of vancomycin or less (Watanakunakorn, 1984). A few reports have pointed to the existence of occasional resistant strains (Sewell et al, 1979; Marsik and Brake, 1982) but these have never been adequately characterised. There is no evidence that the emergence of coagulase-negative staphylococci resistant to vancomycin is a problem at present. Vancomycin therefore emerged as the most reliable of the antibiotics tested **in vitro** against coagulase-negative staphylococci causing CAPD peritonitis.

CHAPTER 4

THE ORGANISMS CAUSING CAPD PERITONITIS AND THEIR ANTIBIOTIC SENSITIVITIES

2. Bacteria other than Coagulase-Negative Staphylococci*

Summary: We tested the antibiotic sensitivities of 32 strains of bacteria other than coagulase-negative staphylococci isolated from infected dialysate. Gram positive isolates were tested against vancomycin, rifampicin, netilmicin and cefamandole and Gram negative isolates against netilmicin, tobramycin, gentamicin, cefamandole, cefuroxime and cefotaxime. Vancomycin and rifampicin were active against all ten Gram positive isolates. Netilmicin was active against 19 of the 22 Gram negative isolates; gentamicin and tobramycin were each active against 18; and cefuroxime was active against only seven. We determined that a combination of vancomycin and either netilmicin, tobramycin or gentamicin would be the best initial treatment of CAPD peritonitis from the bacteriological point of view.

Introduction

In the previous chapter, evidence was presented that vancomycin was the most consistently active antibiotic against the most common causative organism, the coagulase-negative staphylococcus. Other generally active agents were rifampicin, netilmicin and cefamandole. Cefuroxime, the drug of choice for the

* Part of the data in this chapter has been published in Nephron. See Appendix 4.

initial treatment of CAPD peritonitis at the Queen Elizabeth Hospital, emerged extremely badly, with more than half the strains tested being resistant to it. On this evidence alone, it was clear that cefuroxime would have to be replaced.

The next step in choosing the best available antibiotics for initial treatment was to consider in turn the antibiotic sensitivities of the other Gram positive and Gram negative isolates.

Materials and Methods

Samples of infected CAPD dialysate were obtained and cultured as previously described (p 60). Isolates were identified using conventional techniques. Antibiotic sensitivities were determined using the Stokes disc diffusion method (Stokes and Ridgway, 1980). The Gram positive isolates other than coagulase-negative staphylococci were only tested against the four antibiotics consistently active against the coagulase-negative staphylococci viz, vancomycin, rifampicin, netilmicin and cefamandole. The antibiotics tested against the Gram negative isolates were netilmicin, gentamicin, tobramycin, cefamondole, cefuroxime and cefotaxime. (Neither vancomycin nor rifampicin has satisfactory activity against many Gram negative bacteria.)

Results

During the twelve months from 1 May 1982 to 30 April 1983, there were 75 episodes of CAPD peritonitis. Organisms were isolated from dialysate on 71 of the 75 occasions (95%). One species was cultured on 65 occasions and two on five occasions. There were 43 isolates of coagulase-negative staphylococci, whereas no other organism was cultured on more than four occasions (Table 4.1).

Gram Positive Isolates Other Than Coagulase-Negative Staphylococci

Vancomycin and rifampicin were both active against all ten isolates; cefamandole was active against all except the three **Strep. faecalis** isolates; netilmicin, however, was only active against the **Staph. aureus** and diphtheroid isolates. These findings were combined with those of the previous chapter. Overall activity of the four antibiotics against all the Gram positive isolates was therefore vancomycin, 100%; rifampicin, 98%; cefamandole, 91%; and netilmicin, 85%.

Gram Negative Isolates

Netilmicin was the most consistently active antibiotic tested, inhibiting all but three of the 22 isolates (**Klebsiella aerogenes, Agrobacterium** sp and an unidentified aerobic Gram negative bacillus). Gentamicin and tobramycin were both active against 18 of the 22 isolates and cefotaxime against 16. Cefuroxime and cefamandole were each only active against seven isolates.

Overall Antibiotic Sensitivities

These are shown in Table 4.2. The best single agent was netilmicin, active against 86% of isolates. However, combinations of vancomycin with netilmicin and vancomycin with tobramycin or gentamicin provided activity against 96% and 95% of isolates respectively. Cefuroxime, the drug of choice at the start of the study, was active against only 47% of isolates.

TABLE 4.1

BACTERIA ISOLATED FROM DIALYSIS EFFLUENT DURING 71 EPISODES OF CAPD PERITONITIS

Organism	Number of Isolates
Coagulase negative staphylococci	43
Other Gram positive organisms	10
Streptococcus viridans	4
Strep. faecalis	3
Staphylococcus aureus	2
Diphtheroid	1
Gram negative bacteria	22
Klebsiella aerogenes	4
Enterobacter spp	4
Acinetobacter spp	3
Pseudomonas aeruginosa	3
Serratia marcescens	2
Escherichia coli	1
Proteus mirabilis	1
Agrobacterium sp	1
Other aerobic Gram negative bacilli	3
Total	75

TABLE 4.2

OVERALL SENSITIVITIES OF 76 ISOLATES FROM EFFLUENT FROM CAPD PATIENTS WITH PERITONITIS

Antibiotic	Number of Sensitive Isolates	Number of Resistant Isolates	Percentage Isolates Sensitive
Vancomycin and Netilmicin	73	3	96
Vancomycin and Gentamicin/ Tobramycin	72	4	95
Netilmicin	65	11	86
Cefamandole	56	20	74
Cefuroxime	36	40	47

Discussion

This analysis showed that no single antibiotic had a spectrum of activity wide enough for it to be used alone with confidence in the initial treatment of CAPD peritonitis at the Queen Elizabeth Hospital. Netilmicin emerged as the best agent overall but, like all aminoglycosides, it has very little activity against streptococci. As streptococci can cause severe peritonitis (p 44), it is essential that they should be effectively treated from the outset. Cefamandole (and hence the similar cephalothin) emerged as a fair choice against Gram positive isolates, although poorly active against **Strep. faecalis.** However, it was inactive against most of the Gram negative isolates. The third generation cephalosporin, cefotaxime, was not considered for use against Gram positive isolates as it is poorly active against staphylococci. It faired better against the Gram negative isolates but was nevertheless inactive against **P. aeruginosa** and **Acinetobacter** spp. Cefuroxime was no more effective against Gram negative isolates than against coagulase-negative staphylococci.

The logical conclusion of this survey was to combine vancomycin, which has outstanding activity against Gram positive organisms with netilmicin, tobramycin or gentamicin, each of which would be active against most Gram negative organisms, including **P. aeruginosa.** Such a combination would be active against about 95% of organisms causing CAPD peritonitis. It would also be synergistic against many Gram positive strains (Garrod et al, 1981).

The number of isolates of most species other than coagulase-negative staphylococci tested in this analysis is small. However, the isolates tested are representative of the organisms causing CAPD peritonitis everywhere (p 23) and their sensitivities agree closely with those found in much larger studies of the same species (Garrod et al, 1981). The present analysis is thus likely to hold good for the treatment of CAPD peritonitis elsewhere. Nevertheless, several recent reports indicate that treatment of CAPD peritonitis is still often begun with antibiotics which have little or no activity against many likely causative organisms. A survey of renal units using CAPD in the United Kingdom at the end of 1982 highlighted this (Gokal and Marsh, 1984). Table 4.3 shows the antibiotic(s) used to start treatment by the 41 renal units surveyed. Only five of the protocols would be likely to achieve a high degree of success. It was therefore not surprising that Gokal and Marsh found that "often treatment of peritonitis was unsuccessful" and "50% of units reported 5-15% of episodes of peritonitis had become intractable".

Keogh and others (1983) used netilmicin alone and found that netilmicin resistant streptococci caused three of the 14 episodes of peritonitis they studied. Krothapulli and others (1983) began treatment with intravenous vancomycin alone. They did not discuss the outcome of the 23% of their infections caused by Gram negative organisms. Raman and Maskell (1985) report that only 68% of 168 episodes of CAPD peritonitis were cured by cephradine, a cephalosporin with a spectrum of activity somewhat narrower than that of cefuroxime.

TABLE 4.3

ANTIBIOTICS USUALLY GIVEN BY INDIVIDUAL RENAL UNITS FOR PERITONITIS BEFORE KNOWLEDGE OF INITIAL DIALYSATE CULTURE RESULTS
(ADAPTED FROM GOKAL AND MARSH, 1984)

Single Agents		Combinations	
Cefuroxime	- 12	Cefuroxime + Gentamicin	- 5
Cefotexime	- 3	*Cefuroxime + Netilmicin	- 1
Gentamicin	- 2	Cefuroxime + Tobramycin	- 1
Cephradine	- 1	Cefuroxime + Cotrimoxazole	- 1
Vancomycin	- 1	Cephradine + Tobramycin	- 1
		*Cephalothin + Gentamicin	- 1
		Amoxycillin + Flucloxacillin	- 1
		*Vancomycin + Gentamicin	- 1
		†*Vancomycin + Tobramycin	- 1
		Cefamandole + Flucloxacillin	- 1
		Flucloxacillin + Gentamicin	- 1
		Cefuroxime + Ampicillin + Flucloxacillin	- 2
		*Cefuroxime + Netilmicin + Vancomycin	- 1
		Amoxycillin + Flucloxacillin + Tobramycin	- 1
		Other Combinations	- 3

* Treatment judged to give adequate initial cover

†* Treatment at Queen Elizabeth Hospital

Having made our selection of antibiotics on the basis of **in vitro** tests, the next step was to design a treatment protocol which would combine maximum effectiveness with minimum risk and inconvenience to the patient. This will be considered in the following chapter.

CHAPTER 5

THE TREATMENT OF CAPD PERITONITIS: A COMPARISON BETWEEN CEFUROXIME AND VANCOMYCIN PLUS TOBRAMYCIN

Summary: Of 27 episodes of CAPD peritonitis initially treated with intraperitoneal cefuroxime, only 14 (52%) were cured without recourse to other antibiotics. Eight of the 13 failures were caused by coagulase-negative staphylococci. Three patients developed **Clostridium difficile** colitis during treatment. Subsequently, treatment was started with intraperitoneal vancomycin and tobramycin. Normally, treatment was continued with only the more appropriate of the two antibiotics once the causative organism was known. Thirty-eight episodes of CAPD peritonitis were thus treated. Thirty-one (82%) were cured, including 21 of the 22 infections caused by coagulase-negative staphylococci, but only five of the nine infections caused by Gram negative organisms. Intraperitoneal vancomycin plus tobramycin thus appeared a more effective initial treatment of CAPD peritonitis than cefuroxime. However, serum concentrations of tobramycin were sometimes potentially ototoxic and the regimen was judged too complicated for routine use at home.

Introduction

In the previous chapter, we saw that the combination of vancomycin and an aminoglycoside was active **in vitro** against almost all the organisms commonly causing CAPD peritonitis. Both vancomycin and the aminoglycosides are potentially ototoxic and are normally excreted almost exclusively by the kidneys. As they are poorly dialysed, they must be used with caution in patients in renal failure. It was quickly recognised that intraperitoneal administration is the most effective way of ensuring that the bacteria causing CAPD peritonitis are exposed to lethal concentrations of the aminoglycosides, whilst the patient is relatively shielded from their ototoxic effects (p 45). Evidence for the potential ototoxicity of intraperitoneal aminoglycoside regimens in current use has already been presented (pp 45-48). However, no reports of ototoxicity occurring in patients treated for CAPD peritonitis had been published by mid-1982. Vancomycin has also been reported to cause ototoxicity. Cases are, however, rare and have only been associated with serum concentrations of vancomycin in excess of 50 mg/l (Moellering et al, 1981). There is no evidence that vancomycin potentiates the ototoxicity of the aminoglycosides.

A satisfactory intraperitoneal aminoglycoside regimen must be a compromise between the conflicting requirements of antimicrobial efficacy and safety. Most aminoglycoside-sensitive organisms are inhibited by 2 mg/l or less of gentamicin or tobramycin (Garrod et al, 1981). Whilst ototoxicity may occur when peak serum concentrations are as low as 5-8 mg/l (Smith et al, 1980), data on the pharmacokinetics of intraperitoneal aminoglycosides in patients with CAPD peritonitis were still sparse in 1982. De Paepe and others (1981) treated three patients with gentamicin 7.5 mg/l of dialysate for three weeks. The concentration of gentamicin in the drained dialysate remained above 2 mg/l whereas serum concentrations rose to a maximum of 4-5 mg/l after several days. Williams and others (1982) studied serum concentrations of tobramycin in 20 patients with CAPD peritonitis. Each received an intravenous "loading dose" of 1.7 mg/kg bodyweight followed by 8 mg/l of dialysate. They found that the mean serum concentration after seven days of treatment was 6 mg/l. The range of concentrations was not given. As bacteraemia associated with CAPD peritonitis is very rare unless the infection is extremely severe, we saw no great virtue in the loading dose as a routine measure. We therefore elected to give the aminoglycoside only by intraperitoneal injection, in the hope of achieving the rather lower serum concentrations reported by De Paepe and his colleagues.

Gentamicin and tobramycin have virtually identical antibacterial activity, except that gentamicin is slightly the more active against **Staph. aureus** and tobramycin against **P. aeruginosa** (Garrod et al, 1981). Tobramycin has proved less ototoxic in laboratory animals but the evidence in human studies is inconclusive (Smith et al, 1980). Netilmicin appears somewhat more active and less ototoxic than either gentamicin or tobramycin but in 1982, it cost twice as much as the other two. On balance, therefore, we selected tobramycin as it was cheaper than gentamicin in the Queen Elizabeth Hospital at that time.

Most Gram positive bacteria are inhibited by 4 mg/l of vancomycin or less, whereas vancomycin ototoxicity is unlikely unless serum concentrations exceed 50 mg/l. Vancomycin thus seems to offer a wider margin of safety than the aminoglycosides. The organisms most likely to cause rapidly fatal peritonitis are **Staph. aureus** and streptococci (Fenton et al, 1981). To ensure immediate cover against these organisms, we elected to give an intravenous loading dose of 500 mg of vancomycin followed by 15 mg/l of dialysate intraperitoneally thereafter. At the time the study was initiated, no data were available on the serum concentrations likely to result from this regimen.

It was envisaged that both antibiotics would normally be given only until the results of culture were known. Thereafter, the more appropriate antibiotic would be continued alone for a period (arbitrarily chosen) of 12-14 days. As the majority of isolates were Gram positive, most infections would be treated with vancomycin, the less toxic antibiotic. As very few episodes were now culture negative, treatment with both antibiotics for 14 days would be exceptional.

Given the very poor showing of cefuroxime, both clinically and in our laboratory studies, we felt that we could not justify starting a prospective randomised controlled trial comparing cefuroxime with vancomycin and tobramycin. This chapter thus describes the results of treating 38 consecutive episodes of CAPD peritonitis with vancomycin and tobramycin and retrospectively compares these with 27 episodes treated with cefuroxime.

Patients and Methods

All the episodes of CAPD peritonitis seen between March 1982 and February 1983 were included in the study except for ten episodes randomly allocated for treatment with Augmentin during August-September 1982 (Gruer et al, 1983a). Samples of dialysate were taken and processed as previously described, with antibiotic sensitivities being tested by the Stokes method (p 86). Treatment was started as soon as bacteriological samples had been taken.

Regimen 1 : March - September 1982

After an initial intravenous dose of cefuroxime 500 mg, cefuroxime 150 mg was added to every 2 litre bag of dialysate for 12 days. If isolates were resistant to cefuroxime, another appropriate antibiotic was given.

Regimen 2 : October 1982 - February 1983

After an initial intravenous infusion of vancomycin 500 mg, vancomycin 30 mg and tobramycin 16 mg were added to every bag of dialysate until the results of bacteriological culture and antibiotic sensitivities were known (usually 48-72 hours). Thereafter, treatment was continued as follows:-

(1) vancomycin sensitive organisms: vancomycin 30 mg added to each bag of dialysate;

(2) vancomycin resistant, tobramycin sensitive organisms: tobramycin 16 mg added to each bag of dialysate;

(3) organisms resistant to both vancomycin and tobramycin: treatment with another appropriate antibiotic started;

(4) if no organisms cultured despite other evidence of peritonitis, treatment with vancomycin and tobramycin continued.

Treatment was normally given for a total of 12-14 days.

Under both regimens, patients were only treated in hospital if they were systemically unwell. Patients admitted to hospital were treated as above, unless they had severe abdominal pain which did not settle quickly. In such circumstances, rapid peritoneal lavage (see p 36) was started and continued until symptoms improved. Patients treated at home were carefully instructed by renal unit staff how to inject antibiotics into fresh dialysate. They were reviewed in the CAPD clinic after two and ten days treatment and in all cases their administration tubing was changed after two days of treatment.

Treatment failure: Treatment was considered to have failed if the causative organism was not eradicated after the course of treatment or if peritonitis due to the same organism recurred within 28 days of the end of treatment.

Antibiotic concentrations: Serum vancomycin concentrations were assayed using an Abbott TDX immunoassay system (Abbott Diagnostics Divisions, Queensborough, Kent, UK). Serum tobramycin concentrations were assayed using an EMIT immunoassay system (Syva UK Ltd, Maidenhead, Berkshire, UK).

Statistical analysis: The statistical significance of differences was tested by the Chi squared test with Yates' correction.

Results

Treatment with cefuroxime: The 27 episodes of CAPD peritonitis treated with cefuroxime are summarised in Table 5.1. Only 14 (52%) were cured. Eight of the 13 failures were caused by coagulase-negative staphylococci. Only two of these eight failures were caused by organisms reported to be resistant to cefuroxime whilst all eight were resistant to flucloxacillin (methicillin). All of the seven successfully treated episodes caused by coagulase-negative staphylococci were reported to be sensitive to cefuroxime,

TABLE 5.1

TREATMENT OF 27 EPISODES OF CAPD PERITONITIS WITH CEFUROXIME

Organism	Number of Infections	Sensitive to Cefuroxime	Cured by Cefuroxime	Cured by Vancomycin	Cured by Tobramycin	Catheter Removed
Coagulase negative staphylococci	15	13	7	8/8	-	0
Streptococcus spp	3	2	2	1/1	-	0
Gram negative bacilli	8	5	4	-	2/4	1
Culture negative	1	?	1	-	-	0
Total	27	21	14	9/9	2/4	1

but two were resistant to flucloxacillin. Thus, disc sensitivity to flucloxacillin seemed a better indicator of the outcome of treatment with cefuroxime of infections caused by coagulase-negative staphylococci than did disc sensitivity to cefuroxime itself (13/15 vs 9/15). The reasons for this have been discussed on page 71. All eight infections caused by coagulase-negative staphylococci which did not respond to cefuroxime were ultimately cured by vancomycin.

Only four of the eight infections caused by Gram negative bacilli were cured by cefuroxime. Two of these four failures were subsequently cured by tobramycin.

Treatment with Vancomycin and Tobramycin

The 38 episodes treated with vancomycin and tobramycin are summarised in Table 5.2. Thirty-one episodes (82%) were cured by the vancomycin/tobramycin regimen. All the isolates of coagulase-negative staphylococci were sensitive to vancomycin and all but one of the 22 infections they caused were cured by vancomycin. The single failure also did not respond to clindamycin and the organism only disappeared when the patient developed peritonitis due to **Klebsiella pneumoniae**! Two infections involving vancomycin sensitive diphtheroids did not respond to vancomycin. One responded when ampicillin was added but the other was only cured by removal of the intraperitoneal catheter.

Only five of the nine infections involving Gram negative organisms were cured without recourse to other antibiotics. The unsuccessfully treated infections were caused by **P. aeruginosa** (2), **Proteus vulgaris** and **Klebsiella pneumoniae.** Only the Klebsiella

TABLE 5.2

TREATMENT OF 38 EPISODES OF CAPD PERITONITIS WITH VANCOMYCIN AND TOBRAMYCIN

Organism	Number of Infections	Sensitivity to		Cure	Cure with other Antibiotics	Catheter Removed
		Vancomycin	Tobramycin			
Coagulase negative staphylococci	22	22	12	21	0	0
Diphtheroid	2	2	2	1	0	1
Gram negative bacillus	7	-	6	4	3	0
Staph. aureus + Ps. aeruginosa	1	1/2	2/2	0	0	1
Acinetobacter sp + coagulase negative staphylococcus	1	1/2	1/2	1	0	0
Diphtheroid + coagulase negative staphylococcus	1	2/2	2/2	0	1	0
Culture negative	4	?	?	4	0	0
Total	38	36		31	5	2

was resistant to tobramycin and was eradicated by a combination of amikacin and cefotaxime. The infections caused by the **Proteus** and one of the **Pseudomonas** isolates were cured by combining tobramycin with azlocillin. The second **Pseudomonas** infection was only cured by removal of the intraperitoneal catheter.

Comparison of the Two Regimens

Overall, treatment with vancomycin/tobramycin appeared much more successful than that with cefuroxime (31/38 vs 14/27). However, both regimens registered only moderate success against Gram negative organisms (5/9 vs 4/8). The main difference lay in the results of treatment of coagulase-negative staphylococci (21/22 vs 7/15; $X^2 = 9.03$, $p < 0.005$).

Twenty-seven of the 38 patients receiving vancomycin/tobramycin (71%) and 17 of the 27 patients receiving cefuroxime (63%) were treated entirely as out-patients. Four of the patients treated with cefuroxime as out-patients had persistent coagulase-negative staphylococcal peritonitis for several weeks before responding promptly to vancomycin. All the patients treated at home with vancomycin/tobramycin responded promptly.

Three of the patients treated with cefuroxime developed colitis due to **Clostridium difficile** which was successfully treated with oral vancomycin. No adverse effects were noted in the patients treated with vancomycin and tobramycin.

Serum Concentrations of Vancomycin and Tobramycin

These were each measured in six patients after five to 14 days' treatment. Vancomycin concentrations ranged from 8 to 12 mg/l (mean 10.1) and tobramycin concentrations from 3.1 to 4.8 mg/l (mean 3.6).

Discussion

Cefuroxime was the most popular antibiotic for the initial treatment of CAPD peritonitis in the United Kingdom, at least until the end of 1982 (Gokal and Marsh, 1984). There are no data to indicate whether or not this situation has changed. However, the present study confirms **in vivo** the impression already gained **in vitro** that cefuroxime is not a suitable antibiotic for the initial treatment of CAPD peritonitis. Only about half the infections were cured without recourse to other antibiotics, and three patients developed **Cl. difficile** colitis. Other authors have reported similar results. Gokal and others (1982) successfully managed only 62% of episodes with cefuroxime alone. They also reported that **Cl. difficile** colitis developed in 13 of their cefuroxime treated patients, of whom two survived only after total colectomy and one died. Raman and Knight (1985) found that cefuroxime cured only 55% of 29 episodes of CAPD peritonitis.

The outstanding **in vitro** activity of vancomycin against Gram positive organisms was mirrored by its success in eradicating all but one coagulase-negative staphylococcus and two diphtheroids in the 27 episodes involving Gram positive organisms (89%). Furthermore, all eight of the episodes caused by coagulase-negative staphylococci which did not respond to cefuroxime were cured by vancomycin. Another promising account of the use of intraperitoneal vancomycin has recently been published (Gray et al, 1985). Doses of 50 mg/l of vancomycin and 50 mg/l of ceftazidime, a new cephalosporin, were added to each bag of dialysate. The less appropriate antibiotic was stopped when the causative organisms were identified and treatment was continued for seven to 14 days. Sixty-three of 64 episodes of CAPD peritonitis were cured including all those caused by Gram positive bacteria. Krothapalli and others (1983) reported that vancomycin 1g given intravenously once weekly for four weeks successfully cured 82% of 62 episodes of CAPD peritonitis. However, theirs and the present study are not strictly comparable. Fifty-seven per cent of their episodes were caused by **Staph. aureus** and only 25% by coagulase-negative staphylococci compared with 3% and 63% respectively in the present study.

Treatment of Gram negative infections with tobramycin was less successful. As only nine such infections were treated with tobramycin during the study, we were unable to determine whether it was more effective than cefuroxime. However, all but one of the Gram negative isolates were sensitive to tobramycin whereas several, including the **P. aerugoinosa** isolates, were totally resistant to cefuroxime. At the very least, therefore, tobramycin emerged as an effective antibiotic for holding at bay most Gram negative infections until culture and antibiotic sensitivity results were known.

Since 1982, various other ways of treating CAPD peritonitis have been recommended (Fenton, 1982; Editorial, 1982; Vas, 1983). However, few authors have presented for scrutiny the results of their treatment. Adequate assessment is thus impossible. The studies of cefuroxime have been presented above. Glasson and Favre (1984) used intraperitoneal cotrimoxazole to treat 45 episodes of peritonitis, of which 85% were cured. However, our study of isolates of coagulase-negative staphylococci suggests that it is highly unlikely that such a good result could have been achieved in our patients. Maskell and Crump (1985) used cephradine 500 mg six hourly by mouth for seven days as their standard treatment of 168 episodes. Only 68% responded and "intractable peritonitis", requiring catheter removal, developed in 14%. Their poor results can be readily explained. Firstly, cephradine has poor activity against many strains of coagulase-negative staphylococci (p 78) and is inactive against many Gram negative bacteria including **Enterobacter, Serratia** and **P. aeruginosa** (Garrod et al, 1981). Secondly, although cephradine is usually well absorbed when taken by mouth, its penetration into the peritoneal cavity may be less satisfactory, particularly when the peritoneal membrane is not acutely inflamed. To my knowledge, there are no published studies of the intraperitoneal penetration of oral cephradine in patients with CAPD peritonitis (Gruer, 1985). My own pilot study of treatment of CAPD with oral Augmentin (amoxycillin plus clavulanic acid) was similarly unsuccessful (Gruer et al, 1983a). This antibiotic combination has a spectrum of activity substantially wider than that of cephradine. I concluded then that there was no oral antibiotic which could be confidently used for the initial treatment of CAPD peritonitis.

The serum concentrations of vancomycin did not exceed 12 mg/l in any of our patients and hence were well below the concentrations of greater than 50 mg/l which are believed to be potentially ototoxic. However, serum concentrations of tobramycin were between 3 and 5 mg/l in all patients. As previously discussed (p 45), such concentrations may be toxic in some patients, particularly if maintained for long periods, or attained repeatedly in patients requiring multiple courses of treatment. The following question thus arises: can the use of the aminoglycoside be modified, to reduce the serum levels attained without compromising the efficacy of the treatment?

The majority of patients successfully treated themselves with vancomycin and tobramycin at home. However, the 12 day regimen proved rather poorly adapted to this purpose. If both antibiotics are added to all bags for three days followed by one antibiotic for a further nine days, 60 separate injections are required. Vancomycin is only available in ampoules of 500 mg diluted in 20 mls. Exactly 1.2 ml of this solution must be withdrawn to ensure a dose of 30 mg. Tobramycin is available as a solution of 40 mg/ml and hence 16 mg will be provided by 0.4 ml. Hence, the regimen demands considerable diligence and accuracy from the patient. A second question thus arises. Can the treatment be simplified without compromising its efficacy?

An attempt to resolve these two questions is presented in the following section.

CHAPTER 6

THE TREATMENT OF CAPD PERITONITIS WITH ONCE-DAILY VANCOMYCIN AND GENTAMICIN*

Summary: One hundred episodes of CAPD peritonitis were treated by adding antibiotics to the overnight dialysate only for nine days. Treatment was started with vancomycin and gentamicin and continued with the more appropriate agent once culture results were known. Eighty-eight episodes were cured by a single course of treatment. All but two of the 70 infections caused by Gram positive organisms were cured by these antibiotics alone. However, other antibiotics were required in eight of the 19 infections involving Gram negative bacteria. The intraperitoneal catheter had to be temporarily removed only twice. Seventy-six episodes were treated entirely at home and on only eight occasions did the patient spend more than one night in hospital because of peritonitis. Serum vancomycin concentrations during treatment were below 12 mg/l. Serum gentamicin concentrations were usually around 3 mg/l but occasionally higher. Two cases of gentamicin induced ototoxicity have since occurred using this treatment. An effective alternative to the aminoglycosides is required.

* A summary of these results has been published as a letter in the Lancet. See Appendix 4.

Introduction

In Chapter 5, we showed that the vancomycin/tobramycin regimen was an effective means of treating most episodes of CAPD peritonitis. However, the need for frequent, accurately prepared injections made it impractical for self-administration. Furthermore, serum concentrations of tobramycin sometimes attained potentially ototoxic levels. It struck us that the regimen could be readily simplified by decreasing the frequency of injections but increasing the unit dose. The causative organisms would thereby be exposed intermittently to higher concentrations of antibiotics. During the undosed periods, previously absorbed antibiotics would slowly diffuse back into the peritoneal cavity. This would ensure both that the bacteria were still being exposed to antibiotics, albeit in low concentrations, and that some elimination of the antibiotics occurred. Thus, serum antibiotic concentrations would follow a wavelike rather than a flat curve. Substantiation of this idea came from Manchester, where Professor G E Mawer (unpublished observations) developed a computer model of the pharmacokinetics of intraperitoneal gentamicin, based upon the data of De Paepe and others (1981) and Pancorbo and Comty (1981). From these, he deduced that a once-daily intraperitoneal dose of 1 mg/kg bodyweight would lead to peak and trough serum concentrations of 5 mg/l and 2 mg/l respectively. In 1982, Baird and Jones published a short report of the use of 10 mg/l of intraperitoneal gentamicin or netilmicin given **twice** daily. They found this regimen was bacteriologically satisfactory in most cases of CAPD peritonitis and led to maximum serum antibiotic concentrations of 2.9 mg/l in the one patient studied.

Encouraged by this information, we established a simplified regimen whereby 100 mg of vancomycin and/or 40 mg of gentamicin were added to the overnight bag of dialysate only, for nine days. Gentamicin was used because at the start of the study it had become appreciably cheaper than tobramycin. The antibiotics were added to the overnight bag to ensure a dwell time of at least seven hours. The doses of antibiotics were chosen both to ensure satisfactory intraperitoneal and serum concentrations and to take account of the commercially available ampoule sizes.

In this chapter, I describe the results of the use of this regimen in the treatment of 100 consecutive episodes of CAPD peritonitis. Serum and dialysate concentrations of vancomycin and gentamicin obtained in selected patients are also presented, and the cost of this and the previous regimen are compared.

Patients and Methods

The study included all patients with CAPD peritonitis presenting at the Queen Elizabeth Hospital from 1 February 1983 until 100 episodes had been treated. The diagnosis of peritonitis was made and samples of dialysate were taken and processed as previously described (p 60).

Treatment: After dialysate samples had been taken, vancomycin 100 mg (one-fifth of an ampoule) and gentamicin 40 mg (one ampoule) were added to the first fresh bag of dialysate and thereafter to each overnight bag only. Patients who were systemically ill were admitted to hospital. In addition to the first intraperitoneal dose, such patients also received single intravenous doses of vancomycin, 500 mg and gentamicin, 80 mg. Patients with severe abdominal pain were treated with peritoneal lavage until the pain improved. Other patients were treated at home and normally seen at the CAPD out-patient clinic after two and nine days of treatment. If the dialysate was very turbid, heparin 1,000 units was added to each bag of dialysate for 48 hours. The administration tubing was changed after two days of treatment in all cases.

When the results of culture and antibiotic sensitivity were known, treatment was continued as follows:

1. Vancomycin sensitive organisms: vancomycin 100 mg added to the overnight bag only;
2. Vancomycin resistant, gentamicin sensitive organisms: gentamicin 40 mg added to the overnight bag only;
3. Organisms resistant to both vancomycin and gentamicin: another appropriate antibiotic added to all bags;
4. If no organism was cultured, despite a firm clinical diagnosis of peritonitis, vancomycin 100 mg and gentamicin 40 mg were added to the overnight bag only.

Treatment was normally continued for nine days. Each ampoule of vancomycin provided five doses and hence a full course of vancomycin required two ampoules. Ampoules were kept at 4^{o}C while in use.

Treatment failure: Treatment was considered to have failed if the causative organism was not eradicated after the course of treatment or if peritonitis due to the same organism recurred within 28 days of the end of treatment.

Antibiotic concentrations: Serum and dialysate effluent samples were assayed for vancomycin and gentamicin concentrations.

TABLE 6.1

CAUSATIVE ORGANISMS AND RESULTS OF TREATMENT OF 100 CASES OF CAPD PERITONITIS

Causative Organism	Number of Infections	Cure with Once-Daily Treatment	Relapse	Cure with Other Antibiotics	Catheter Removed
Coagulase negative staphylococci	38	34	3	0	1
Coagulase negative staphlococci and another organism	5	5	0	0	0
Staphylococcus aureus	11	10	0	1	0
Streptococcus spp	11	11	0	0	0
Diphtheroids	5	5	0	0	0
Enterobacteriaceae	3	3	0	0	0
Acinetobacter spp	2	1	0	0	1
Pseudomonas spp	5	1	2	2	0
Mixed aerobic Gram negative infection	2	1	0	1	0
Bacteroides fragilis	1	0	0	1	0
B. fragilis + E. coli	1	0	0	1	0
Culture negative	16	16	0	0	0
Total	100	87	5	6	2

Serum samples were taken between 10.00 and 13.00 hours to ensure peak or near peak concentrations were measured. Dialysate effluent samples were collected on days 2, 5 and 9 of treatment. All samples were stored at -70^{o}C until assayed. Concentrations were measured as previously described (p 99).

Results

The 100 episodes were treated between 1 February 1983 and 31 March 1984. During this period, 79 patients underwent CAPD for a total of 560 patient months. The causative organisms and the results of their treatment are shown in Table 6.1. All the Gram positive isolates were sensitive to vancomycin. Sixty-six of the 70 infections involving Gram positive organisms (94%) were cured by the once daily treatment. One infection caused by coagulase-negative staphylococci relapsed once, another twice and a third was cured only by temporary catheter removal. One **Staph. aureus** infection was cured only when oral flucloxacillin was given to treat a concurrent exit-site infection.

Five of the 19 Gram negative isolates were resistant to gentamicin. These and three other isolates failed to respond to gentamicin. Two gentamicin resistant **Pseudomonas** spp responded to cefotaxime. An **Acinetobacter calcoaceticus** was only sensitive **in vitro** to latamoxef. Treatment with this agent was unsuccessful and temporary catheter removal was required. The two infections involving **Bacteriodes fragilis** (clinically appendicitis and diverticulitis respectively) were successfully treated with metronidazole. Two infections caused by gentamicin-sensitive

Pseudomonas spp relapsed after gentamicin was stopped. A severe infection involving **E. coli, Strep. pyogenes** and **Strep. faecalis** was successfully treated with gentamicin, vancomycin and cefuroxime.

The sixteen culture negative episodes all responded rapidly to the once daily treatment. In two of the 16 cases, no sample was sent for culture; in one, the sample was only cultured after two days; in three, the patient had received antibiotics shortly before the sample was taken. In the remaining ten cases, there was no obvious explanation for the negative cultures.

Home or hospital treatment: Seventy-six of the 100 episodes were treated entirely at home. On seven occasions, the patient arrived at the hospital late at night and remained in hospital until the following day. On four occasions, the patient remained in hospital for reasons other than peritonitis (pneumonia, investigation of pulmonary infiltrates, drug induced arthropathy and retraining in CAPD technique). Five episodes developed in hospital, four of them within five days of the insertion of the intraperitoneal catheter. On only eight occasions was the peritonitis severe enough to require hospital admission. The organisms responsible for these severe episodes are shown in Table 6.2. Only one episode, caused by **Acinetobacter calcoaceticus** had been unsuccessfully treated at home. On the other seven occasions, the patient's clinical condition had been severe enough to warrant treatment in hospital from the outset.

Antibiotic concentrations: The mean vancomycin concentrations in serum and dialysate effluent samples from five patients are shown in Table 6.3. The highest recorded serum vancomycin

TABLE 6.2

CAUSATIVE ORGANISMS AND TREATMENT OF EIGHT EPISODES OF CAPD PERITONITIS REQUIRING HOSPITAL ADMISSION

Causative Organisms	Other Treatment Used
Acinetobacter anitratus	Catheter removed
Coagulase negative staphylococcus	Catheter removed
Staphylococcus aureus	Intermittent peritoneal dialysis
E. coli + Strep. pyogenes + Strep. faecalis	Intermittent peritoneal dialysis
E. coli + B. fragilis	Metronidazole + cefotaxime
Viridans streptococcus	None
Viridans streptococcus	None
Coagulase negative staphylococcus	None

TABLE 6.3

MEAN VANCOMYCIN CONCENTRATIONS (mg/l) IN SERUM AND DIALYSIS EFFLUENT FROM FIVE PATIENTS

	Day 2	Day 5	Day 9
Serum	6.1	5.9	6.7
Dosed effluent	14.5	14.5	29.3
Undosed effluent	1.6	2	2.4

concentration in any patient was 12.0 mg/l. The vancomycin concentration in the dosed effluent appeared higher on day 9 than on days 2 and 5, although the differences were not statistically significant. This may reflect a reduction in vancomycin absorption as the peritoneal membrane became less inflamed. Very little vancomycin diffused into the undosed dialysate.

Mean serum gentamicin concentrations were 2.5 mg/l (SD ± 1.2 mg/l) after nine or ten days treatment in seven patients. The highest recorded serum gentamicin concentration was 5.0 mg/l. The mean gentamicin concentration in 18 bags of dosed effluent from nine patients during their first three days of treatment was 4.6 mg/l (range 2.4 - 11.6 mg/l). Gentamicin was undetectable in most bags of undosed effluent with the highest recorded concentrations being 2.2 mg/l.

No adverse effects attributable to the antibiotics were observed.

Total dosage and cost of treatment: Table 6.4 compares the total dose of antibiotic administered and the cost of the two vancomycin/aminoglycoside regimens. This shows that both total dose of antibiotic and cost were substantially reduced by the once-daily treatment, which also usually required only 13 injections compared with the 60 given previously.

Discussion

The addition of vancomycin and/or gentamicin to only the overnight bag proved to be no less effective than the addition of lower doses of vancomycin and tobramycin to all bags. The once-

TABLE 6.4

TOTAL DOSAGE AND COST OF TREATMENT OF CAPD PERITONITIS WITH ONCE-DAILY AND FOUR-TIMES DAILY INTRAPERITONEAL VANCOMYCIN AND GENTAMICIN

	Once Daily[1]		Four Times Daily[2]	
	Total Dose (mg)	Cost[3] (£)	Total Dose (mg)	Cost[3] (£)
Full course vancomycin	1,000	25.04	1,940	50.68
+ 3 days gentamicin	120		272	
3 days vancomycin	300	19.41	860	39.56
+ full course gentamicin	400		848	

1 vancomycin 100 mg/bag
gentamicin 40 mg/bag
10 day course

2 vancomycin 500 mg and gentamicin 80 mg IV x 1
then vancomycin 30 mg/bag, gentamicin 16 mg/bag, 12 day course

3 Current NHS prices: vancomycin 500 mg - £11.09
(1983) gentamicin 80 mg - £1.70

daily regimen cured 87% of episodes compared with the 82% success achieved by its all-bag predecessor. Furthermore, only two of the 100 episodes treated by the once-daily regimen required temporary catheter removal.

The treatment of infection caused by Gram positive organisms was, once again, extremely successful. As before, all the Gram positive isolates were sensitive to vancomycin. In only one of the 70 episodes was another antibiotic used and in only one case was the intraperitoneal catheter removed. Whether or not the aminoglycoside given during the first two or three days contributes to these good results remains to be established. However, many of the staphylococci were extremely sensitive to gentamicin and tobramycin. Vancomycin and gentamicin or tobramycin act synergistically against many staphylococci and streptococci, including strains resistant to the aminoglycoside alone (Garrod et al, 1981). Aminoglycosides are also rapidly bactericidal in peritoneal dialysate whereas vancomycin acts more slowly (Bint et al, 1980; Loeppsky et al, 1983; Ziezler et al, 1956; Wilcox et al, 1985). The initial combination may thus be an important factor in ensuring the success of the once-daily treatment of Gram positive organisms.

Treatment of Gram negative infections was less successful. Only six of the 14 infections caused by Gram negative organisms were cured by the once-daily treatment. Four of the failures were caused by **Pseudomonas** spp, organisms which other workers have also found difficult to eradicate from the peritoneum (Vas, 1985). Temporary catheter removal was, however, required only once, for an infection caused by a multiply resistant **Acinetobacter**

calcoaceticus. These results lend weight to the idea that CAPD peritonitis caused by **Enterobacteriaceae, Pseudomonas** spp and **Acinetobacter calcoaceticus** might be best treated by a combination of synergistic antibiotics, once the results of culture and sensitivity are known.

Only eight patients had to spend more than one night in hospital because of peritonitis and all but the most severe episodes were treated without changing the patient's dialysis routine. As the once-daily dose was either a single 40 mg ampoule of gentamicin or one-fifth of a 500 mg ampoule of vancomycin, patients found the treatment simple and agreeable to use. The success of home treatment was also warmly welcomed by the staff of the renal unit. Indeed, the rapid expansion of the CAPD service at the Queen Elizabeth Hospital (described in Chapter 8) could not have occurred without it.

Successful home treatment also leads to major financial savings. The cost of treatment has, however, rarely been considered in the published debate on CAPD peritonitis. Beardsworth and Goldsmith (1982) found that the annual cost per CAPD patient of re-admission to hospital was £2,856 in 1979 and only £528 in 1981. They attributed a large part of this reduction to the introduction of a policy of home treatment of peritonitis where possible. Rubin and others (1980) calculated that in 1979 the average cost of treating an episode of CAPD peritonitis was $1,605. Atkins and others (1981c) found that the cost of each episode varied from $1,085 to an astonishing $6,885 when caused by multiply resistant **Staph. aureus.** The present study has shown that most episodes of peritonitis can be treated for about £25 ($30) plus the cost of syringes and laboratory investigations.

Our study of antibiotic concentrations in dialysate and serum revealed large inter-patient variations for both vancomycin and gentamicin. This variation has been noted by other workers for vancomycin (Pancorbo and Comty, 1982; Bunke et al, 1983), gentamicin (Pancorbo and Comty, 1981), tobramycin (Bunke et al, 1982) and netilmicin (Keogh et al, 1983; Grefberg et al, 1984). Studies of the peritoneal clearance of vancomycin or aminoglycoside given intravenously also substantiate our findings that these antibiotics diffuse rather unpredictably from the blood stream into the peritoneal cavity. Glew and others (1982) found that after intravenous administration, dialysate concentrations of vancomycin ranged from 0-96% of simultaneous serum concentrations, with an average value of 27%. Bunke and others (1982 and 1983) calculated that on average only 15-20% of an intravenous dose of either vancomycin or tobramycin was cleared by CAPD.

The reasons for the wide variations in peritoneal absorption and clearance of vancomycin and the aminoglycosides remain poorly understood. Such variations have been observed both in patients with peritonitis (Glew et al, 1982; Magera et al, 1983; Keogh et al, 1984) and in those without (Pancorbo and Comty, 1981 and 1982; Bunke et al, 1982 and 1983; Paton et al, 1983). As our results for vancomycin suggest, it is possible that the degree of inflammation of the peritoneal membrane influences diffusion, but this does not seem to be the major determinant. The importance of factors such as the surface area and micro-circulation of the peritoneal membrane has yet to be assessed.

Given the relatively unpredictable absorption of these antibiotics, it does not seem very useful to employ dosage schedules based on body-weight, as some authors have recommended (Bunke et al, 1982 and 1983). Such an approach greatly complicates treatment and will inevitably lead to mistakes and wastage of antibiotics. A fixed dose regimen is preferable, provided that it delivers sufficient antibiotic to the site of infection to eliminate all infective organisms but insufficient to the eighth cranial nerve to poison the patient. The present regimen appeared to meet the first requirement in most cases as judged by the clinical results. We also found that concentrations of vancomycin and gentamicin in the dialysate exceeded the minimum inhibitory concentration against most organisms throughout the overnight dialysis period. The second requirement was also certainly satisfied for vancomycin. Serum concentrations of vancomycin never exceeded 12 mg/l, well below the potentially toxic range (Farber and Moellering, 1983). Our data for gentamicin were, however, less reassuring: some patients developed serum gentamicin concentrations of 4-5 mg/l. Although none of the patients in this study developed symptoms of ototoxicity, other published data strongly indicate that such concentrations are potentially ototoxic (Mawer et al, 1974; Lerner et al, 1983).

Confirmation that ototoxicity can result from our once daily regimen came several months after completion of the present study. Two patients who had received several courses of once-daily intraperitoneal gentamicin in quick succession developed clinically apparent vestibular toxicity. Fortunately, however, symptoms gradually subsided once the gentamicin had been stopped. Serum gentamicin concentrations were not measured.

Given the rather mediocre performance of gentamicin and tobramycin in our two studies plus their potential toxicity, what are the alternatives? Netilmicin is believed to be less ototoxic than either gentamicin or tobramycin (Lerner et al, 1983) and is more active against many staphylococci and some strains of Gram negative bacilli (Moellering, 1983). Two studies of its use in the treatment of CAPD peritonitis have been published. Keogh and others (1984) treated 14 episodes of peritonitis with continuous intraperitoneal netilmicin in doses ranging from 5-20 mg/l of dialysate. There were only five Gram negative isolates and two of these were resistant to netilmicin. Vestibular toxicity developed in one patient receiving 20 mg/l of netilmicin (an imprudently high dose, in my view). Her serum netilmicin concentrations reached 15 mg/l after only two days of treatment. Grefberg and others (1984) treated 23 episodes in 18 patients. They added 30 mg of netilmicin to each of the first eight 2 litre bags and then 30 mg to each overnight bag thereafter for a further six days. Twenty-three episodes were treated; five were "un-evaluable" and 16 were cured. All four episodes caused by Gram negative organisms were cured. Commendably, all 18 patients were tested audiometrically as soon as possible after admission and one and three months thereafter. Auditory function remained unchanged in all patients but, on the last day of treatment, one patient developed severe vertigo which lasted for two months. These studies are too limited to suggest whether or not netilmicin is more effective than gentamicin or tobramycin in treating Gram negative CAPD peritonitis. They make it clear, however, that, like all available aminoglycosides, netilmicin is potentially ototoxic.

The most promising candidate among the new cephalosporins is ceftazidime which has excellent activity against most Gram negative bacilli, including, importantly, **P. aeruginosa** (Gozzard et al, 1983). It has, however, less activity against several other species of **Pseudomonas** and **Acinetobacter** and the staphylococci (Gould and Wise, 1985). A study of the use of ceftazidime and vancomycin has recently been published (Gray et al, 1985). In a series of 64 cases of CAPD peritonitis, seven of the eight episodes known to have been caused by Gram negative bacteria were cured by intraperitoneal ceftazidime. These promising results have prompted my colleagues in the renal unit at the Queen Elizabeth Hospital to embark upon a prospective study using intraperitoneal vancomycin and ceftazidime.

Other possibilities for the future include members of the quinolone family of antibiotics such as pefloxacin and norfloxacin. These agents have a spectrum of activity similar to that of ceftazidime although streptococci are relatively resistant. They appear to have few side effects (although clinical experience is limited) and they do not induce the development of resistant strains as readily as the new cephalosporins (Editorial, 1984; Gould and Wise, 1985).

In conclusion, this study has shown for the first time that most episodes of CAPD peritonitis can be effectively and safely treated at home by the once-daily addition of antibiotics to the dialysate. However, the aminoglycoside remains an imperfect choice for which a substitute should be sought. Furthermore, it is essential that the use of this, and any other, treatment of CAPD peritonitis should be kept under constant scrutiny to ensure that its effectiveness is being maintained.

CHAPTER 7

DISINFECTION OF THE HANDS AND TUBING OF CAPD PATIENTS*

Summary: The effectiveness of two methods of handwashing before the bag exchange was studied over a three month period in 31 patients using CAPD. A defined, double rinse with 70% ethanol was found to be more convenient and much more effective than povidone iodine detergent alone or povidone iodine followed by 70% ethanol. Spraying the tubing around the bag connector with 70% ethanol reduced the number of adherent skin organisms and hence the likelihood of bacteria being drawn into the dialysate. Although there was no difference in the overall incidence of peritonitis in the two study groups, there was an unexpected drop in the incidence of peritonitis caused by coagulase-negative staphylococci. This was attributed to an increased overall awareness of the importance of handwashing and aseptic procedures during the bag exchange. Patients whose catheter exit sites were colonised with **Staph. aureus** or **Acinetobacter** spp were found to be likely to develop peritonitis due to these organisms.

* The data presented in this chapter has been published in the Journal of Hospital Infection. See Appendix 4.

Introduction

Since CAPD was first introduced, it has been universally agreed that bacterial contamination of the dialysate occurs most readily during the dialysis exchange. Organisms present on the patients' hands, on the connector itself or in the surrounding air are thought to enter the system while the connector is disconnected. All patients are therefore trained to wash their hands thoroughly before each bag exchange (Clayton et al, 1981). An antiseptic detergent is generally recommended, the commonest being povidone iodine (Betadine), and chlorhexidine (Hibiscrub). Although the effects of these agents have been studied on the hands of health-care personnel (Ayliffe, 1980), their effect on the resident flora of patients' hands has not been evaluated. At the start of the study, all our patients were using povidone iodine. We have therefore compared its effectiveness as a hand disinfectant with that of 70% ethanol, another widely used skin disinfectant. We also looked at decontamination of the connector and the adjacent tubing and of the skin around the catheter exit site and recorded the incidence of peritonitis during the study.

Materials and Methods

The study took place during a three month period between February and May 1983. The 31 patients practising CAPD at the Queen Elizabeth Hospital, Birmingham, were each randomly allocated to one of two groups. Group A contained 16 patients and Group B 15. The groups were found to be matched in terms of age, sex, time on CAPD, previous episodes of peritonitis and proportions of diabetics to non-diabetics. All patients used the "Travenol IIR" system, and carried out three or four exchanges per 24 hours.

Skin disinfection before bag exchange: Hands were disinfected before preparation of the surface, administration set and bag, and immediately prior to exchange. Group A patients continued to use the existing method, consisting of a thorough handwash with povidone iodine detergent ("Betadine" surgical scrub) followed by an application of 5 ml of 70% ethanol containing 1% glycerol as an emollient. Group B patients applied 5 ml of 70% ethanol and 1% glycerol to the cupped hands and gently rubbed until dry. The process was then repeated. A defined procedure was taught to ensure all surfaces of hands were covered (Ayliffe, Babb and Quoraishi, 1978). Group A used a non-medicated soap and Group B 4% chlorhexidine detergent ("Hibiscrub") for general handwashing.

Group A cleaned the catheter exit site with povidone iodine detergent and Group B with chlorhexidine detergent. Both groups wore masks during the exchange and Group B also sprayed the outer surface of the bag connector and adjacent tubing with 70% ethanol.

Bacteriological sampling: Samples were taken from the hands, the catheter exit site and the administration tubing at monthly intervals where possible, or in most cases two to four times during the study.

Samples were taken from the hands before and after disinfection using the two methods.

(1) Broth sampling. The tips of the fingers and thumb of one hand were gently kneaded for one minute on the bottom of a Petri dish containing 10 ml of recovery medium. The recovery medium contained nutrient broth

(No 2, Oxoid Ltd, Basingstoke) with a 0.75% lecithin-tween mixture and 1% sodium thiosulphate to neutralise residual povidone iodine or chlorhexidine. Neat and ten-fold dilutions were then drop-pipetted on to the surface of blood and phenolphthalein disodium phosphate (PPD) agar plates. The agar (Oxoid No 2) was enriched with 1% horse serum.

(2) Finger streaks. This method was used to estimate the number of bacteria readily detachable from each finger tip. The fingers and thumb of the other hand were streaked across the surface of a nutrient agar plate (PPD).

The skin of the abdominal wall immediately adjacent to the exit site was sampled using (1) a contact plate (25 cm^2) containing either PPD or blood agar, (2) a swab moistened in Ringer's solution which was then plated directly on to blood and PPD agar.

Swabs moistened in Ringer's solution were used to sample both the bag and peritoneal catheter connectors and also the tubing for 4-5 cm on each side of the connectors. A further sample was taken from Group B patients from the bag connector and adjacent tubing following disinfection with alcohol.

Swabs moistened in Ringer's solution were taken from the anterior nares and cultured immediately on PPD agar.

In the event of a CAPD patient presenting with a bag containing turbid fluid which was found to have more than 100 leukocytes/mm^3, the dialysate was cultured as follows: 20 ml were centrifuged and the deposit plated out on blood and cystine lactose electrolyte deficient (CLED) agar plates; 60 ml were added to a 100 ml medical flat bottle containing 20 ml of sterile nutrient broth (Oxoid No 2) at four-times normal strength, the addition of the dialysate thereby diluting the broth to the correct concentration.

All plates and broth cultures were incubated aerobically at 37°C for 18 hours. Plates were re-incubated for 24 hours at room temperature to assist with identification of coagulase-negative staphylococci and counts were made where appropriate. Strains were identified by conventional tests and the API system was used for all Gram negative bacilli and selected coagulase-negative staphylococci from patients with peritonitis.

Statistical analysis: The difference of means and the Chi-squared test with Yates' correction were used where appropriate.

Results

In Group A, one patient was transferred to haemodialysis before he could be sampled, and another was unable to attend the sampling clinic. The 14 remaining patients were sampled on a total of 36 occasions. The 15 patients in Group B were sampled on 49 occasions.

Hand sampling: The number of resident skin bacteria recoverable from the fingers by the broth sampling method before skin disinfection varied considerably from patient to patient in both groups (range: $1.8 \times 10^2 - 7.2 \times 10^6$ CFU). However, median counts in the two groups were very similar (1.6×10^4 and 3.3×10^4 CFU).

Using the broth sampling technique, there was an increase in the mean bacterial counts following the use of povidone iodine alone and povidone iodine followed by alcohol. These increases were 107% and 51% respectively. There was, however, a mean reduction in the bacterial count of 69% in the defined double alcohol wash group. Thus, the defined alcohol wash led to a significantly greater reduction than either povidone iodine alone or povidone iodine plus alcohol ($p < 0.001$). More resident bacteria were recovered after than before washing with povidone iodine alone on 16 of 29 occasions (55%) and on 12 of 36 occasions (33%) with povidone iodine and alcohol. On five occasions, the bacterial count after povidone iodine and alcohol increased more than five-fold. On only five of the 47 occasions (11%) did the bacterial count rise following the defined alcohol wash, the greatest increase being 3.6 fold.

Table 7.1 shows that with the finger streak sampling method, lower bacterial counts were also obtained following the defined alcohol wash. The alcohol wash led to significantly lower counts being obtained from the thumb, middle and ring fingers.

Bacterial species: The bacteria isolated from the hands were mainly coagulase-negative staphylococci. **Staph. aureus** was recovered from the hands before disinfection in five Group A patients on a total of eight occasions and from seven Group B patients on eleven occasions. Following disinfection, **Staph. aureus** could still be isolated from four of the five Group A patients and two of the Group B patients. These differences were not statistically significant. The following Gram negative bacilli were recovered from 11 of the 83 samples (13%) before disinfection, but none of the samples after disinfection: **Acinetobacter** spp,

TABLE 7.1

EFFECTIVENESS OF HAND DISINFECTION PRIOR TO BAG EXCHANGE: FINGER-STREAK SAMPLING

	Number of Patients Sampled (Fingers)	Range of Bacterial Counts	Percentage of Fingers
After two applications		No growth	60.5
of alcohol	43	1-10	33.5
(Group B)	(215)	11+	6.0
After povidone iodine		No growth	39.3
Group A	29	1-10	28.3
	(145)	11+	32.4
After povidone iodine		No growth	45.2
and alcohol	31	1-10	29.0
(Group A)	(155)	11+	25.8

eight samples from six patients; **Proteus mirabilis,** from two patients and **Escherichia coli,** from one patient. On only three occasions did the number of Gram negative bacilli recovered from a broth sample exceed 100. A few colonies of **Strep. viridans** were recovered from one of the 83 pre-disinfection samples.

Exit site and tubing: Contact plate sampling of the exit site gave very similar counts in both the chlorhexidine and the povidone iodine treated groups. Counts ranged from less than ten colonies to confluent growth, but in both groups there was a moderate to heavy growth in about 70% of samples and a very heavy or confluent growth in 20%. Again, most of the organisms cultured were coagulase-negative staphylococci. However, exit site samples from three patients in Group A and four patients in Group B yielded **Staph. aureus. Staph. aureus** was also grown from the hands before disinfection and the anterior nares in all these patients. Phage typing showed that all strains isolated from different sites in the same patient were identical. **Acinetobacter** spp were isolated from four of the six patients from whose hands they had been recovered. **Proteus mirabilis** was cultured from the exit site of one patient.

The results of sampling the administration tubing before and after spraying with 70% alcohol are shown in Table 7.2. This shows that there was more contamination of the tubing around the peritoneal catheter connector, which lies close to the abdominal wall, than around the bag connector. Spraying the tubing around the bag connector with alcohol led to a large reduction in counts, with 82% of samples taken after disinfection showing no growth.

Peritonitis: Over the three months before the start of the

TABLE 7.2

CONTAMINATION OF THE ADMINISTRATION TUBING BEFORE AND AFTER DISINFECTION WITH 70% ALCOHOL

	Pre-disinfection Samples (%)		Post-disinfection Samples (%)
Bacterial Counts in Range	Peritoneal Catheter Connector	Bag Connector	Bag Connector
0	14	26	82
1 - 10	37	57	16
11 - 100	38	17	2
100 +	11	0	0
Sample number	84	35	49

study (period 1), there were 23 episodes of peritonitis during 94 patient-months of CAPD (one episode per 4.1 patient-months). Over the three months of the study (period 2), there were 16 episodes during 106.5 patient-months (one episode per 6.7 patient-months). Seven of the 16 episodes occurred in six Group A patients and nine in six Group B patients. The organisms isolated during the two periods are shown in Table 7.3. The number of patients infected by coagulase-negative staphylococci fell from 11 of 27 during period 1 to only three of 29 during period 2 ($X^2 = 4.39$, $p < 0.05$) rising again to eight of 27 during the three months following the end of the study. The proportion of patients developing peritonitis caused by other organisms did not change significantly.

Discussion

This is the first time that the effectiveness of the handwashing techniques used by CAPD patients has been studied. Most studies of handwashing techniques have been concerned with the removal of traditional bacterial pathogens such as **Staph. aureus** and **Klebsiella** spp which are transiently found on the hands, and have involved health care personnel. However, CAPD peritonitis is often caused by resident skin bacteria, notably the coagulase-negative staphylococci, and the patients themselves usually carry out their bag exchanges. Hence, it is important to know how effective are the patient's disinfection procedures in reducing the resident as well as the transient skin flora.

Our study has shown that the povidone iodine detergent, as used by our patients, is often counter-productive. Far from reducing the resident skin flora on the hands, it led to an

TABLE 7.3

ORGANISMS CAUSING PERITONITIS IN CAPD PATIENTS BEFORE AND DURING STUDY

Organism	Number of Isolates in Period 1 (27 patients)	Period 2 (study period) (29 patients)
Coagulase negative staphylococci	15	2
Coagulase negative staphylococci		
with Staph. aureus	1	0
with Str. viridans	0	1
with diphtheroids	1	0
with Gram negative bacilli	1	0
Diphtheroids	0	1
Staph. aureus	0	3
Str. viridans	0	4
Acinetobacter spp	2	1
Other Gram negative bacilli	1	2
Yeasts	0	1
Unknown	2	1
Total	23	16

increase on more than half the occasions. The use of 70% alcohol immediately after povidone iodine somewhat improved disinfection but in many instances the counts were still higher than before disinfection. The defined double alcohol wash was significantly more effective, with a mean count reduction of 69%. Nevertheless, on a few occasions, counts were still higher after the alcohol wash than before.

There are probably three main reasons for the greater effectiveness of the defined double alcohol wash. First, the povidone iodine preparation, unlike 70% alcohol, is a detergent as well as a disinfectant. Its detergent action brings to the surface bacteria lodged in pores and creases. Second, 70% alcohol kills bacteria more rapidly than povidone iodine (Ayliffe, 1980). Third, the defined wash means that there is less chance that any part of the fingers will avoid disinfection. The finger streak samples showed that the difference between the two methods was greatest on the thumb, middle and ring fingers. Previous work has shown that these areas are often missed during handwashing (Taylor, 1978).

Despite the superiority of the double alcohol wash over povidone iodine and a single application of alcohol, we were unable to show any difference between the two groups in the incidence of peritonitis during the short period of the study. We did, however, observe an unexpected reduction in the overall incidence of peritonitis caused by coagulase-negative staphylococci, with three episodes during the three months of the study compared with 18 episodes during the three months before the study. Because the coagulase-negative staphylococcus is the most likely contaminant of the bag connector, the incidence of coagulase-negative staphylococcal peritonitis is probably a good indicator of the adequacy of bag exchange technique. Although Group A patients were not specifically instructed in handwash techniques during the study, they inevitably became aware that this was what we were studying. Consequently, patients in both groups may well have paid more attention to their exchanges with less contamination of the bag connector as a result. Indeed, current connector design should ensure that the bag exchange can be carried out aseptically, even with dirty hands, provided technique is meticulous.

The alcohol wash was generally preferred by patients. It could be carried out without using a wash-hand basin making it very suitable for travellers and holiday makers. Once learned, the technique was quicker than using povidone iodine detergent. The alcohol, being almost colourless, did not stain clothes or jewellery. With the added glycerol, it was found by some patients to be gentler to the skin than povidone iodine. All patients were thus switched to the defined double alcohol wash once the results of the study were known. Despite this, the incidence of coagulase-negative staphylococcal peritonitis rose sharply again. Was this because some patients had returned to their old slack ways?

The fallability of the handwash procedures would seem to provide a good argument for the use of sterile gloves during the bag exchange. In practice, the benefits of gloves are unlikely to be great. Donning the gloves without contaminating them requires care and dexterity. The patients who would use gloves properly would probably be those with a good exchange technique and hence a low risk of peritonitis. Less competent patients would be less likely to use the gloves to advantage. Given the considerable expense of supplying sterile gloves for every exchange, their use cannot be recommended at present.

Each of the three episodes of **Staph. aureus** peritonitis was caused by organisms identical to isolates previously cultured from the patient's nose, hands and exit site. Those patients who had **Staph. aureus** on their hands but not on the exit site did not develop **Staph. aureus** peritonitis during the study. This perhaps favours the exit site as a focus of colonisation from which direct spread along the outside of the catheter later occurred. Sewell and others (1982) also found a very significant relationship between nasal or skin carriage of **Staph. aureus** and subsequent **Staph. aureus** peritonitis. Carriers of **Staph. aureus** accounted for seven of the eight episodes they studied and three of the four persistent carriers developed **Staph. aureus** peritonitis during the 13 months of their study.

Acinetobacter peritonitis occurred in two of the four patients carrying the organism on their exit site as well as on their hands. A similar strain was found on the face-flannel of one of these patients. Colonisation of the exit site by potential pathogens occurred despite reported daily cleansing of the exit site with either povidone iodine or chlorhexidine detergent. Both these agents thus seem inadequate for the purpose. It may be that the detergent has a damaging effect on the skin which favours colonisation.

Our study showed that **Strep. viridans** is almost never found on the hands or exit site of CAPD patients. The most likely route to the peritoneum taken by these oral organisms is via the blood stream. Two of the four episodes of **Strep. viridans** peritonitis during the study period occurred in the only splenectomised patient in the group. We have subsequently seen four patients all of whom developed **Strep. viridans** peritonitis shortly after developing an oral lesion or undergoing dental treatment (Kiddy et al, 1985). We thus recommend that CAPD patients should use a soft bristle toothbrush to minimise damage to the gums, and attend to oral lesions promptly. Any dental treatment involving the gums should be covered by antibiotic prophylaxis, using the same regimen advised for patients at risk of infective endocarditis (Working party, 1982). Furthermore, as we found no evidence that oral organisms contaminate the bag connector during the exchange, we have dispensed with the mask, thus simplifying the bag changing routine and increasing its social acceptability.

Hand disinfection emerges from this study as a ritual that is at best of limited value and at worst distinctly counter-productive. A defined double alcohol wash is probably the most practical method. Until the foolproof bag exchange is developed, a meticulous aseptic technique will remain the best insurance against infection. In the Epilogue, I shall discuss the progress that is being made towards the ideal exchange.

CHAPTER 8

FOUR YEARS OF CAPD PERITONITIS

Summary: During 1981-1984, 131 patients were trained to use CAPD at the Queen Elizabeth Hospital, Birmingham. Four patients died while on CAPD but only one from peritonitis. The overall incidence of peritonitis was one episode every 5.1 patient-months, being lowest in 1983 but increasing again in 1984. By the end of 1984, 43 patients had used CAPD for more than one year; only seven of these had not had peritonitis and six had had at least ten episodes. CAPD was permanently discontinued following seven of the 319 episodes of peritonitis (2.1%). The intraperitoneal catheter was temporarily removed following a further 5.6% of episodes including 8.8% of those in 1984. As a result, the antibiotic treatment of peritonitis has recently been re-assessed. Peritonitis remains the main threat to the CAPD programme at the Queen Elizabeth Hospital.

Introduction

The antibiotic regimens I have described on the preceding pages have, with certain reservations, proved to be suitable for treating most episodes of bacterial CAPD peritonitis. However, if peritonitis is frequent, then failure to cure even a small percentage of cases can lead to the failure of CAPD for a significant number of patients. In this chapter, I assess the impact of peritonitis on the CAPD programme at the Queen Elizabeth Hospital (QEH) by considering the incidence of peritonitis over four years and the rate of failure of CAPD due to peritonitis.

These results are then compared with those obtained in other centres.

Patients and Methods

All patients trained in CAPD at the QEH between 1981 and 1984 were included in the analysis. All episodes of peritonitis and all temporary and permanent interruptions of CAPD were noted. The peritonitis rate was first calculated simply as "episodes per patient-months of treatment". Then, to allow more accurate comparisons between the peritonitis rate in different populations and at different times, the probability of developing a first episode of peritonitis was calculated by standard life-table analysis (Pierratos et al, 1982; Bradford Hill, 1977). The significance of differences between probability curves was determined by the log-rank test using a Hewlett-Packard programmable calculator. The technique survival of CAPD was calculated by the method of Kaplan and Meier (1958) with patients who stopped CAPD because they died or received a renal transplant being considered "lost to follow-up" from the date of death or transplantation.

Results

During the period January 1981 to December 1984, 131 patients were trained to use CAPD at the QEH. Figure 8.1 compares the increase in the number of patients using CAPD at the hospital during this period with the world-wide increase that occurred in 1979-82. By the end of 1984, patients at the QEH had been using

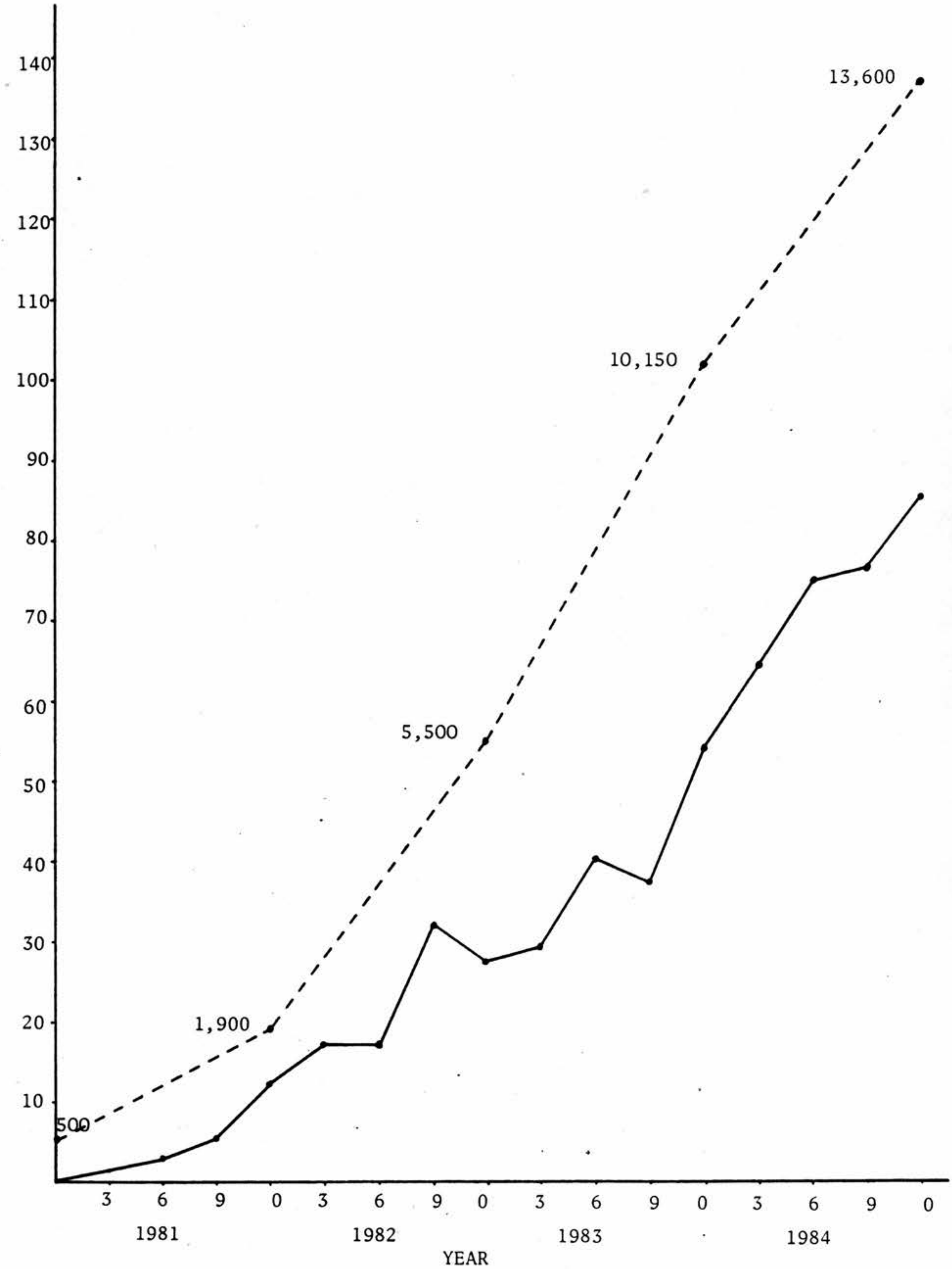

Figure 8.1 Number of patients on CAPD at the end of each three month period at the Queen Elizabeth Hospital, Birmingham, 1981 - 84, and in the world, 1979 - 1982 (----)

CAPD for a mean of 12.4 months. However, Figure 8.2 shows that only one-third of the patients had used CAPD for more than 12 months and only 16 patients had had more than two years' experience. The average age of the patients was 42.4 years (range 15-70). Fourteen patients were aged over 60 years but only two over 65. Ninety patients were male and 41 female; 31 patients were diabetic. During the four years, 30 of the 131 patients received a renal transplant after an average period of 10.2 months of CAPD. Four of the 131 patients died while using CAPD: three from ischaemic heart disease (two within one month of starting CAPD) and one from peritonitis (see below).

Peritonitis

During the total of 1,631 patient-months of CAPD, there were 319 episodes of peritonitis giving an overall incidence of one episode every 5.1 patient-months. The number of patient-months per episode was 3.2 in 1981, 3.9 in 1982, 6.1 in 1983 and 5.4 in 1984. The probability of developing a first episode of peritonitis against time is shown in Figure 8.3. This shows that patients trained in 1983 took significantly longer to develop their first episode of peritonitis than those starting in 1982, whereas in 1984 the peritonitis-free interval shortened again. Figure 8.4 shows that only seven of the 43 patients using CAPD for more than a year had not had peritonitis whilst six had had at least ten episodes.

Only one patient, a 57 year old man, died as a result of peritonitis. This fatal episode was treated in a hosptial outside Birmingham and neither the causative organism nor the treatment given are known. In seven of the 319 episodes (2.1%), peritonitis led to the permanent removal of the intraperitoneal catheter and

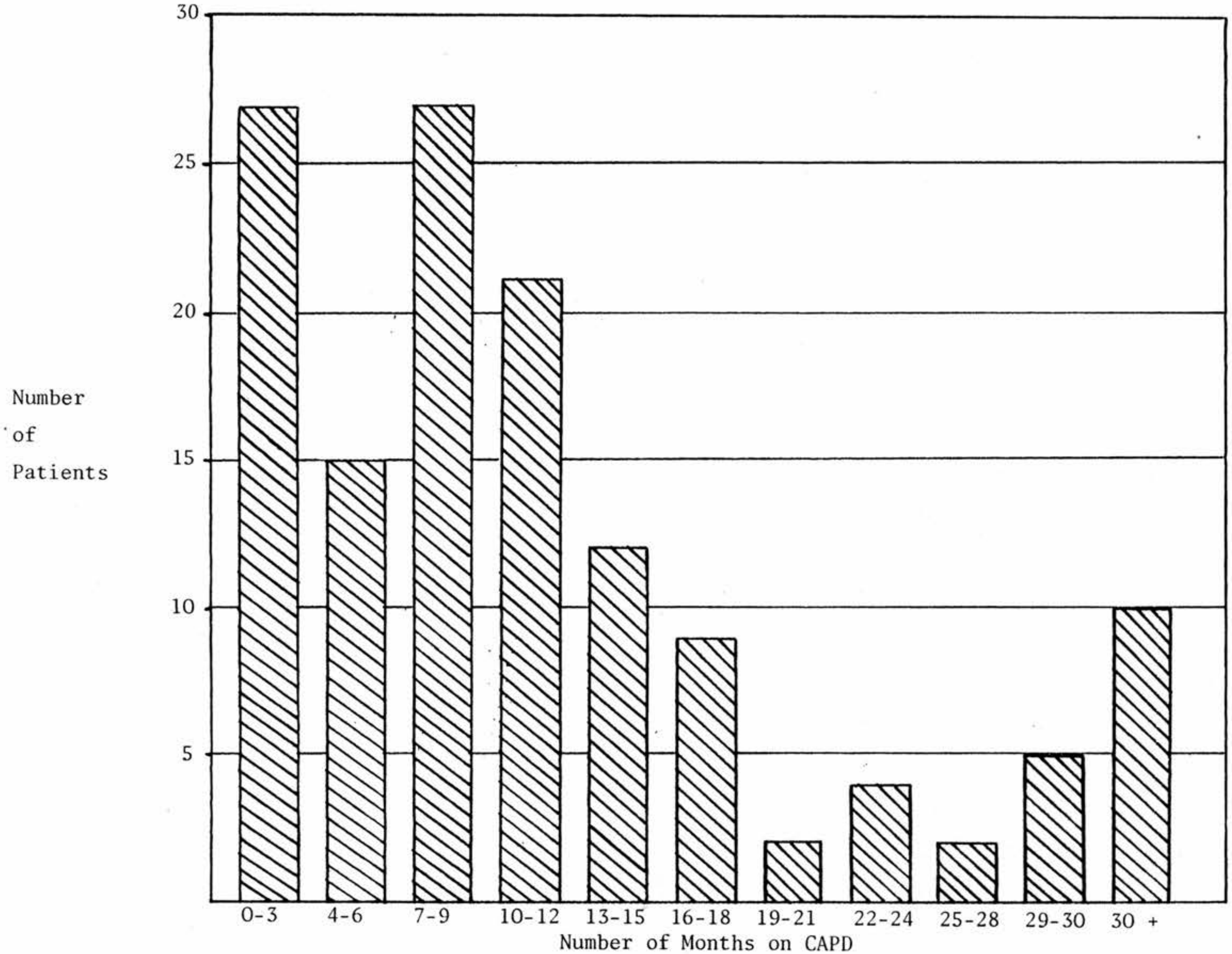

Figure 8.2 Number of months on CAPD of patients on CAPD at the Queen Elizabeth Hospital

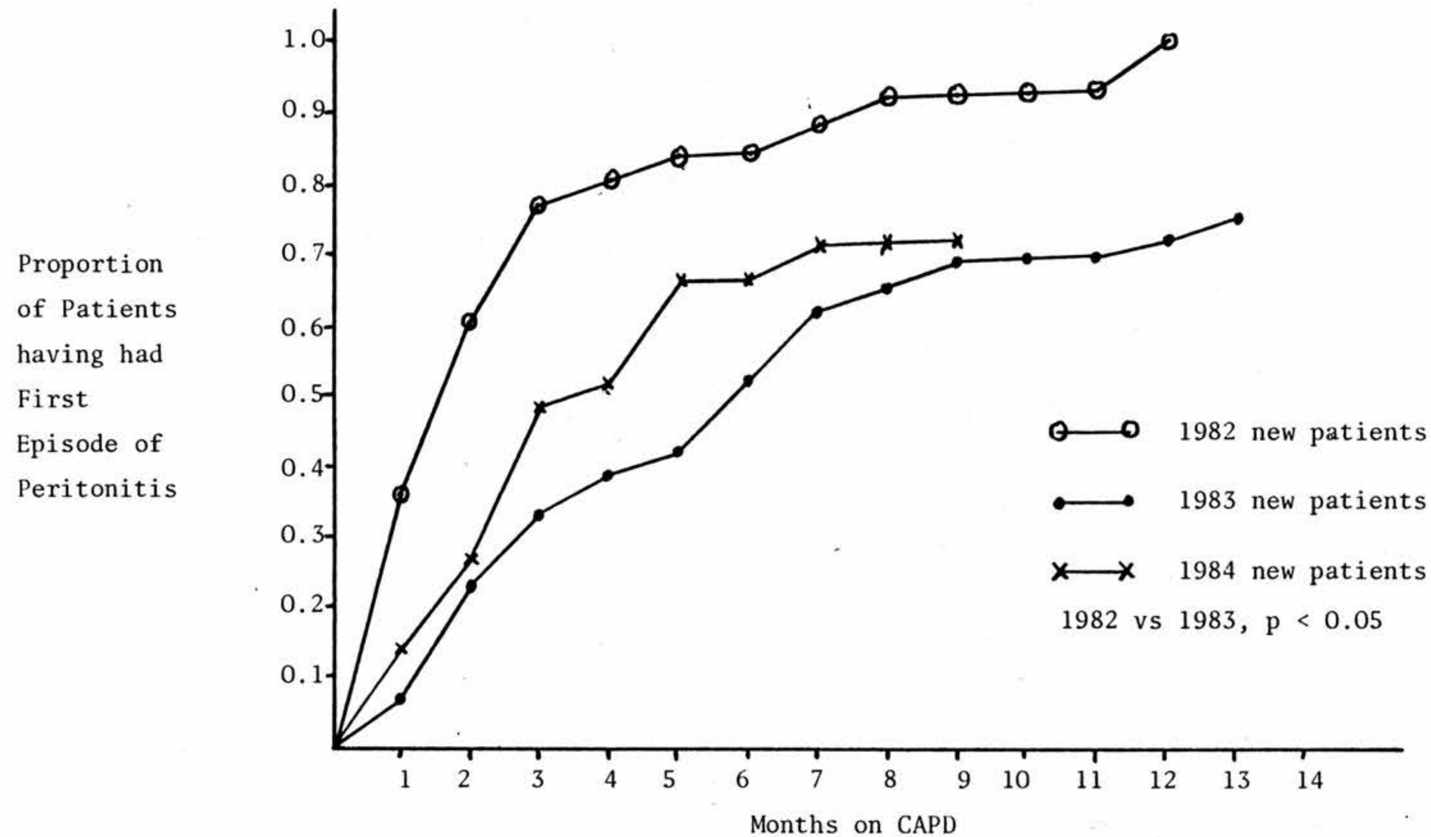

Figure 8.3 Probability of developing first episode of peritonitis

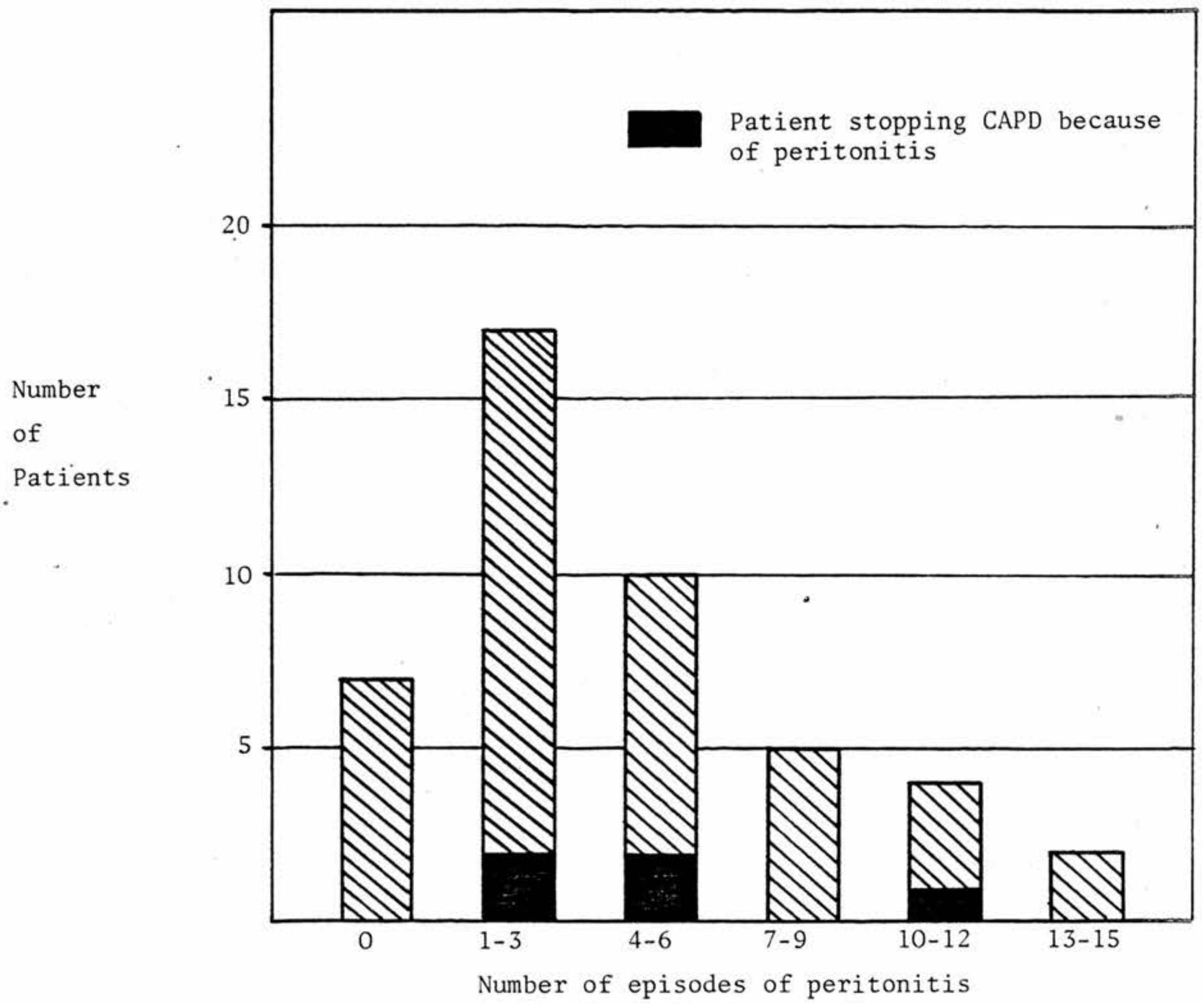

Figure 8.4 The number of episodes of peritonitis experienced by patients who had used CAPD for more than one year

discontinuation of CAPD. In a further 18 episodes (5.6%), the catheter was temporarily removed because of peritonitis but successfully replaced one to three months later. The causative organisms in these 25 cases are shown in Table 8.1 which also shows that in most cases the catheter was removed because of recurrent rather than acute infection. In only two cases did peritonitis lead to the failure of the peritoneum as a dialysis membrane, and in both of these a combination of pyogenic bacteria was responsible. The likelihood of catheter removal did not seem to be related to the patient's age or sex or to the presence of diabetes mellitus. Table 8.2 shows that the frequency with which the intraperitoneal catheter was temporarily removed rose sharply in 1984.

The effect of peritonitis on the long-term success of CAPD is shown in Figure 8.5. Seven per cent of patients had discontinued CAPD because of peritonitis after one year and 16.6% after two years. Of the 11 occasions when CAPD has failed during the first four years of the programme, seven have been due to peritonitis.

Discussion

The remarkably rapid rise in the number of patients using CAPD worldwide between 1979 and 1982 is mirrored in the increase in the number of patients using CAPD at the QEH (Figure 8.1). CAPD patients at the QEH have been younger on average than those in most other centres, with an average age of 42.4 years compared with an average age of 49.5 years in the 3,784 patients on CAPD throughout Europe at the end of 1982 (Moore et al, 1984). Only two patients

TABLE 8.1

THE CAUSATIVE ORGANISMS RESPONSIBLE FOR PERITONITIS LEADING TO TEMPORARY OR PERMANENT PERITONEAL CATHETER REMOVAL IN 25 CAPD PATIENTS

	Temporary Catheter Removal	Permanent Catheter Removal
Due to recurrent infection		
Coagulase-negative staphylococci	6	1
Diphtheroids	2	0
Aerobic sporing bacillus	2	0
Staph. aureus	1	1
Agrobacterium sp.	0	1
Due to severe acute infection		
Yeast	2	0
Enterobacter cloacae	1	0
P. aeruginosa	1	0
Strep. viridans	1	0
Acinetobacter anitratus	1	0
Pseudomonas sp. + *Citrobacter freundii*	0	1
E. coli + *B. fragilis*	0	1
P. aeruginosa + *S. aureus*	0	1
Unknown	1	1
Total	18	7

TABLE 8.2

PATIENT-MONTHS OF CAPD FOR EACH TEMPORARY OR PERMANENT CATHETER REMOVAL

	1982	1983	1984
Temporary catheter removal	136	153	61
Permanent catheter removal	273	229	198

Percentage Failure of CAPD

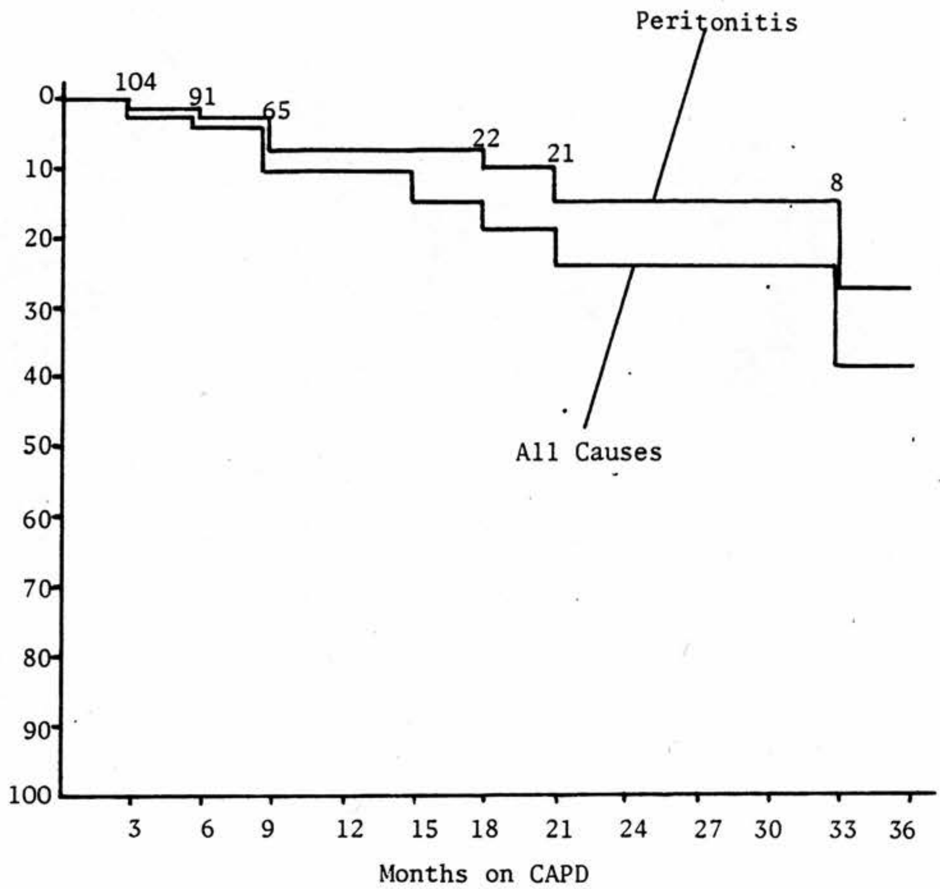

Figure 8.5 Percentage failure rate of CAPD due to (1) peritonitis and (2) all causes

(numbers above steps indicate number of patients still using CAPD at start of each period) at the QEH were aged over 65 years, compared with about 17% of all patients on CAPD throughout Europe. The relative youth of the patients at the QEH may explain in part why their overall survival at two years was about 96.4% (three deaths) compared with only 72% overall throughout Europe (Moore et al, 1984).

The incidence of peritonitis at the QEH and its impact on the CAPD programme remain unacceptably high. The probability of developing peritonitis within the first year of CAPD was 100% in patients starting in 1982 and 1984 (Figure 8.3). Only in 1983 did it drop to 60% to compare more favourably with the results of the most successful centres. The National Institutes of Health reported a probability of 70% in the United States as a whole (Friedman, 1984); in Toronto the figure was 64% (Pierratos, 1982); in Montpellier, using a filter system, 30% (Slingeneyer et al, 1982); and in Milan using a novel disinfectant system, a remarkable 22% (Maiorca et al, 1983). (These latter two systems will be considered in the Epilogue.) The overall incidence of peritonitis at the QEH of one episode every 5.1 patient-months was also much higher than that reported in many centres. The average incidence in the United States during the period 1981-83 was one episode every 7.5 months but a number of experienced centres there have recently reported one episode only every 11-14 months (Multicenter Study Group, 1985). In the United Kingdom, a recent survey found that eight of the 41 contributing units had a peritonitis rate of better than one episode every 12 patient-months. At the other extreme, however, ten centres reported rates of one episode every four months or less (Gokal and Marsh, 1984).

Why have the peritonitis rates at the QEH remained so high when the techniques and equipment used there appear to be the same as those of units where peritonitis is less frequent? Because peritonitis can so readily result from poor patient technique and personal hygiene, its prevention currently depends heavily upon the training given to patients and their supervision thereafter (Clayton et al, 1981). As already described in Chapter 7, the incidence of CAPD peritonitis caused by coagulase-negative staphylococci fell sharply when close attention was paid to patients' bag-exchange technique (Gruer et al, 1984b). Most units have experienced a high incidence of peritonitis in the initial months of their CAPD programme, followed by an improvement as staff become more experienced in training and supervising their patients. This appeared to happen at the QEH between 1982 and 1983 but the situation clearly deteriorated again in 1984. At the QEH in early 1983, the 20-30 CAPD patients were trained and supervised by two full-time nurses. By the end of 1984, the number of patients had increased to nearly 90, but only one more part-time nurse had been assigned to their care. No extra medical staff had been taken on since the CAPD programme had begun. All patients continued to be seen in the same small room (4.5 m x 3 m) that had been allocated for CAPD in 1981. Then it was envisaged that the number of patients in the programme would not exceed ten! Consequently, the amount of time that nursing and medical staff could devote to each patient has dropped progressively and their working facilities have become less adequate. I believe this situation largely accounts for the rise in the incidence of peritonitis at the QEH between 1983 and 1984.

Although efforts to reduce the incidence of peritonitis at the QEH have been unsuccessful, its treatment has been comparatively satisfactory. None of the 318 episodes treated at the QEH was fatal. This compares with a case-fatality rate of 1.9 to 3.4% in the years 1977-82 in the pioneering centres at Toronto (Fenton et al, 1983). Whilst half the 18 patients who died of peritonitis in Toronto were aged over 60 years, the others were in the age groups from which most of the QEH patients were drawn. This suggests that the absence of fatal episodes at the QEH cannot simply be explained by the relative youth of its CAPD population.

Peritonitis led to the permanent discontinuation of CAPD in 1.4% of episodes of peritonitis at the QEH in 1982, and 2.7% in 1983 and 1984. This compares with case-failure rates of 5.7 to 7.5% in Toronto during 1977 to 1982 (Wu et al, 1983), 9.5% in Newcastle (Ramos et al, 1983) and 12% in Mississippi (Rubin et al, 1983). In part, this difference between the QEH results and those of other centres may reflect more appropriate antibiotic treatment. It may also lie in the current readiness at the QEH to remove the catheter temporarily if antibiotics have failed to eradicate the infection. This strategy has proved to be effective in aborting both severe acute infections and milder recurrent ones (Table 8.1).

A notable feature of the 1984 results was the marked increase in the number of temporary catheter removals (Table 8.2). Nine of the 13 temporary removals in 1984 were in response to recurrent infections caused by Gram positive bacteria. This has led to a recent re-assessment of the effectiveness of the once-daily vancomycin regimen. It does now appear that this regimen is sometimes insufficient to eradicate all apparently sensitive bacteria. Consequently, vancomycin is again being added to each bag of dialysate to ensure that the infective organisms are constantly exposed to antibiotics. The total daily dose of vancomycin has also been doubled to 200 mg. Work is also in progress to see whether any of these recurrent infections are caused by vancomycin-tolerant organisms.

Only two of the 131 patients had to discontinue CAPD because peritonitis had so damaged the peritoneal membrane as to make dialysis inadequate (Table 8.1). In both cases the infection had been caused by a combination of pyogenic organisms. On the other hand, several patients have had many episodes of peritonitis without a major deterioration in peritoneal dialysis function. However, Rubin and others (1983b) have shown that a high rate of peritonitis is associated with a small but significant decline in peritoneal dialysis function compared with patients with a low rate of peritonitis. Much still needs to be learned about the response of the peritoneal membrane to infection (Diaz-Buxo, 1984). For example, can anything be done to mitigate the effect of peritonitis, other than promptly treating the infection with appropriate antibiotics? Should the peritoneum be periodically rested to promote its regeneration, or will this increase the risk of adhesions? The relative youth of CAPD means that we simply do not know whether the peritoneal membrane can withstand repeated infective and other insults and support patients for over two decades - as haemodialysis has done (Coles, 1985).

In conclusion, peritonitis remains the major threat to the CAPD programme at the QEH. It seems unlikely that the peritonitis rate will decrease significantly unless:

1) the staff-to-patient ratio and hence the quality of patient training and supervision can be increased;

or 2) technical developments which reduce the risk of peritoneal contamination can be introduced.

In the final section, I shall discuss such technical developments and their promise.

EPILOGUE

CAN WE ELIMINATE CAPD PERITONITIS?

Introduction

It is clear that the rapid diagnosis and treatment of peritonitis are indispensable to the safety of CAPD as it has been practised until now. Might we not envisage, however, a time when technical improvements had led to the virtual elimination of the risk of peritonitis? Over the past four years, intensive efforts have been directed towards achieving this end.

The most vulnerable feature of the standard CAPD system is the connector between the bag of dialysate and the administration tubing. Most attention has therefore been focussed on ways of modifying the connector, either to make contamination less likely, or to ensure that contaminating organisms are destroyed **in situ.** This closing section begins by briefly reviewing the developments which have shown most promise. These involve the use of intraluminal filters, intraluminal disinfectants, ultra-violet irradiation and the "sterile weld" bag exchanger.

A radically different approach to the prevention of peritonitis is based on the premise that the natural defences of the peritoneum against infection are compromised by the presence of large volumes of dialysate. The peritoneum cannot therefore respond adequately to the micro-organisms it encounters. The chapter concludes with a review of research in this area which offers the prospect of future preventive measures.

1. Intraluminal Filters

If it is certain that most episodes of peritonitis follow contamination of the bag connector, the logic of fitting a bacterial filter in the tubing between the connector and the peritoneal cavity is irreproachable. As discussed earlier (p 17), the first advocates of the in-line filter were Slingeneyer and his colleagues in Montpellier, France. The design of their system is shown in Figure P.2 (p 18). Each patient normally used each filter for 10-14 days. In two papers, Slingeneyer and his colleagues (1981, 1982) reported that the average peritonitis rate in their CAPD patients, all of whom used the filter system, was one episode per 31 patient-months when they excluded episodes caused by accidental disconnection of the tubing from the Tenckhoff catheter. These rates were substantially lower than those reported by other centres. They cultured the upstream and downstream sides of used filters and found that 25% of 114 filters cultured were contaminated on the upstream side only, whilst only 3% were contaminated on the downstream side. This provided further evidence that the filter was effectively preventing organisms from entering the peritoneal cavity. Unfortunately, this group did not compare peritonitis rates in their CAPD patients with and without the filter. Indeed, their comparative trial of patients using intermittent peritoneal dialysis with and without a filter showed no difference in the peritonitis rates of the two groups. A suspicion therefore remained that the very low peritonitis rates associated with filter use could be due to other factors. Furthermore, the filters were expensive and bulky. Consequently, few other centres took to their use.

More recently, the Millipore Co have developed the Peridex filter, specifically designed for use in CAPD and much more compact than the earlier model used in Montpellier. The main bacteriological weakness of both models is that micro-organisms can circumvent the filter by growing down the outlet by-pass tube and through the check valve. Poole-Warren and others (1984) tested seven Peridex filter sets for 30 days in conditions designed to duplicate normal CAPD routine, except that the first bag of dialysate used in five of the seven sets had been inoculated with 10^6 CFU of **Serratia marcescens.** They found that the organisms successfully by-passed the filter via the outlet tube on Day 19 in three sets and Day 23 in one. They concluded that the system would be likely to afford protection if changed every two weeks. However, given that they only tested five sets and one orgamism, their conclusions seem premature. Ash and Winchester (1984) studied 33 patients both with and without the Peridex filter. They were all said to have a higher than average rate of peritonitis before they began using the filter. The overall rate of peritonitis fell from one episode every 7.5 patient-months to one every 15.6 patient-months ($p < 0.01$). Like Slingeneyer and others, they found that dialysate upstream to the filter was more often culture positive. The principal weakness of this study was that the patients acted as their own historical controls. At least some of the improvement could have been due to the fact that many patients tend to have less peritonitis once they are well established on CAPD (Multicenter study group, 1985). Nevertheless, the results do suggest that the filter can be useful. However, the main disadvantage of the technique is the fact that each filter costs at least £50 (Ash and Winchester, 1983). If the filter is changed every fortnight, the annual cost per patient of filters alone will be £1,300. If most episodes are treated at home as we recommend, for a cost of around £50 per episode, on cost grounds alone the filter could not possibly be justified except in patients with frequent, life-threatening peritonitis.

2. **Ultraviolet Light**

Ultraviolet light of sufficient intensity rapidly kills most bacteria and yeasts. Travenol Inc, a company which has played a major role in the development of CAPD, has recently introduced a portable, battery-powered ultraviolet source designed to sterilise the bag-tubing connector at each exchange. The fresh bag and tubing connectors are partially coupled, leaving the seal of the bag intact. The connector is then placed within the irradiation chamber of the apparatus. Irradiation at 1500 $mW/sec/cm^2$ is maintained for 3-5 minutes, a dose known to produce complete disinfection, even after gross contamination with organisms that are relatively resistant to ultraviolet light, such as **Candida albicans** (Holmes et al, 1984). After irradiation, the male and female portions of the connector are fully coupled, breaking the bag seal and allowing the dialysate to be run into the peritoneal cavity.

This system has recently been subjected to a well designed controlled, randomised, multi-centre trial (Multicenter study group, 1985). One hundred and sixty-seven patients all initially performed CAPD without the u-v system for at least four months. Thereafter, 93 patients were randomly allocated to a control group and 74 to the test group. After a period of retraining of both groups, the comparative trial lasted for nine months. The results showed that there were no significant differences between the peritonitis rates in the pretrial and trial period in either group or between those of the two groups in either period. Nor were there any major differences in the proportion of episodes caused by the different bacterial species. There was thus no evidence that the u-v system reduced the risk of peritonitis in these patients.

The authors attempted to explain these disappointing results on the following grounds. They noted that the overall peritonitis rates in both test and control group patients was, at one episode every 11-14 patient-months, only about half their national average. They thus postulated that most of the patients had excellent bag exchange technique and that the incidence of peritonitis resulting from connector contamination was already low. They found that some patients had much less peritonitis while using the u-v system than before (although, **ipso facto**, others must have had more peritonitis than before). They therefore concluded that the u-v system might be reserved for use by selected patients with high rates of peritonitis thought due to connector contamination. They further suggested that their study showed that the role of contamination of the connector had perhaps been overstressed and that attention should now be turned to other sources of infection, such as the catheter exit site and the intestine.

3. Intraluminal Disinfection of the Connector

Another approach to the problem of contamination of the connector is to bathe in disinfectant the interior of the connector and the adjacent tubing. The principal disadvantage of this method is the risk of toxicity should the disinfectant be allowed into the peritoneal cavity. Two promising variations on this theme have recently been reported. Buoncristiani and others (1983) developed a Y-tube system (Figure E.1) in which arms A and B are filled with dilute sodium hypochlorite solution between each dialysis exchange. During the bag exchange, an empty bag is attached to arm B and the fresh bag to arm A. The waste dialysate is drained into the empty bag. Fresh dialysate is then run from the new bag into the waste bag to remove remaining disinfectant. The main clamp is then opened and the remaining fresh dialysate is run into the peritoneal cavity. Finally, the main clamp is closed and fresh disinfectant solution is run into the two arms via arm B. Both bags are then removed and replaced with sterile caps until the next bag exchange.

The first results of this method (Buoncristiani et al, 1983) were promising, but the non-randomised study design was too weak to allow firm conclusions to be drawn. Maiorca and others (1983) then published the results of a prospective randomised controlled trial in which 32 patients using the standard Travenol spike connector were compared with 32 patients using the Y-tube system. The peritonitis rate in the control group was one episode per 11.3 patient-months compared with one episode per 33 patient-months in the test group ($p < 0.001$). The only adverse effect of the technique was transient severe abdominal pain which occurred on the eleven occasions (out of over 40,000 exchanges) when the

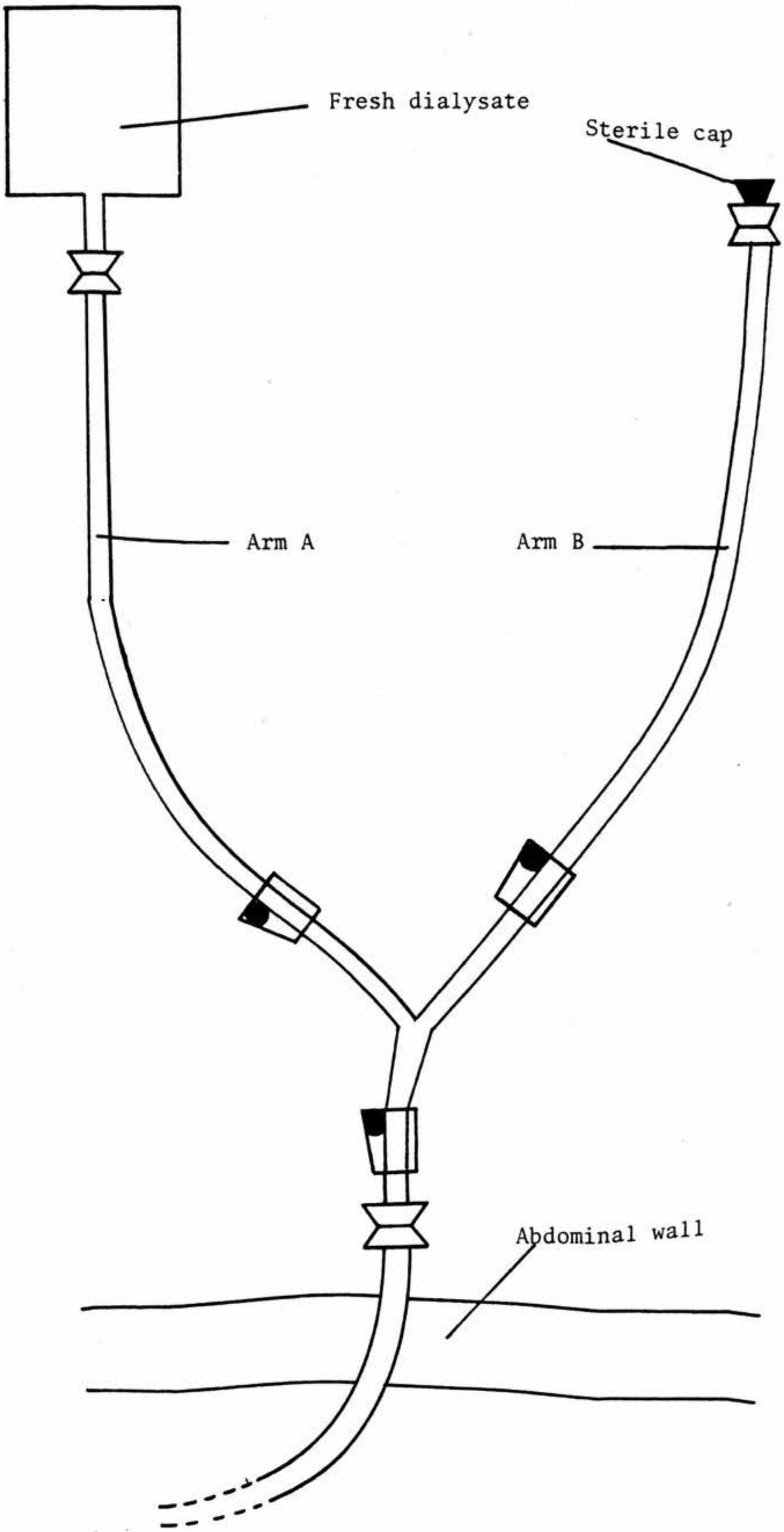

Figure E.1 The Y-tube system

hypochlorite solution was accidentally allowed into the peritoneal cavity. The pain was said to be relieved rapidly by peritoneal lavage and no long term consequences of the incidents were noted.

A simpler approach has been advocated by Parsons and others (1983). Using the conventional Travenol II connector, they simply sprayed a small amount of povidone iodine 5% into the female part of the connector. Thus, when the connection is made, the male portion also becomes bathed in the disinfectant. They reported that after introducing this modification, the peritonitis rate fell from one episode every 4.5-5 patient-months to one episode every 34 patient-months. Further evidence that this simple manoeuvre can effectively prevent peritonitis has been published by Beardsworth and others (1984). Using the Travenol II connector without povidone iodine instillation, the peritonitis rate was one episode every 4.6 months. Povidone iodine instillation was associated with a fall in the rate to one episode every 21.4 patient-months, with the probability of developing a first episode of peritonitis being very significantly reduced ($0.001 < p < 0.002$).

Both the bacterial filter and the u-v light system seem to work well in the laboratory. It is therefore somewhat perplexing that the intraluminal disinfectant systems should give apparently better results. Does this simply reflect different study designs? If not, to what can the differences be attributed? Only further research and, in particular, well designed comparative trials will provide answers to these questions.

Although intraluminal disinfectants can apparently reduce the incidence of peritonitis, their use must be subjected to constant scrutiny. For inevitably, the disinfectant will sometimes be carried into the peritoneal cavity with the attendant risk of toxicity. That this risk is real is shown in a recent paper from Glasgow (Junor et al, 1985). They describe 11 patients who developed sclerosing peritonitis, a severe and irreversible form of peritonitis characterised by the development of a dense layer of fibrous tissue on the peritoneum. All these patients were members of a group of 54 patients who had been spraying the inside of the bag connector with 0.5% chlorhexidine in 70% alcohol. Sclerosing peritonitis did not develop in any of the 107 patients who used 5% povidone iodine in alcohol instead. In vitro studies suggested that the chlorhexidine-alcohol mixture reacts with the intraluminal plastic to produce a suspension of tiny plastic particles. It is not yet clear, however, whether it is the particles or the disinfectant itself which lead to the peritoneal reaction.

4. The Sterile Weld Bag Exchanger

All the systems discussed above require the patient to disconnect and connect their dialysis bags manually. The interior of the connector is thereby exposed to the risk of contamination by skin- and air-borne organisms. Hamilton and others (1983a, b) have described a "sterile weld" system in which the tube leading from the dialysate bag is continuous with the administration tubing. To carry out an exchange, the peritoneum is drained into the waste bag and some of the air in the bag is squeezed back into the first part of the administration tubing. The tubing is then placed within the welding apparatus alongside the tubing of the fresh bag (Figure E.2). An internal "wafer" heats to around 260^{o}C, melting through

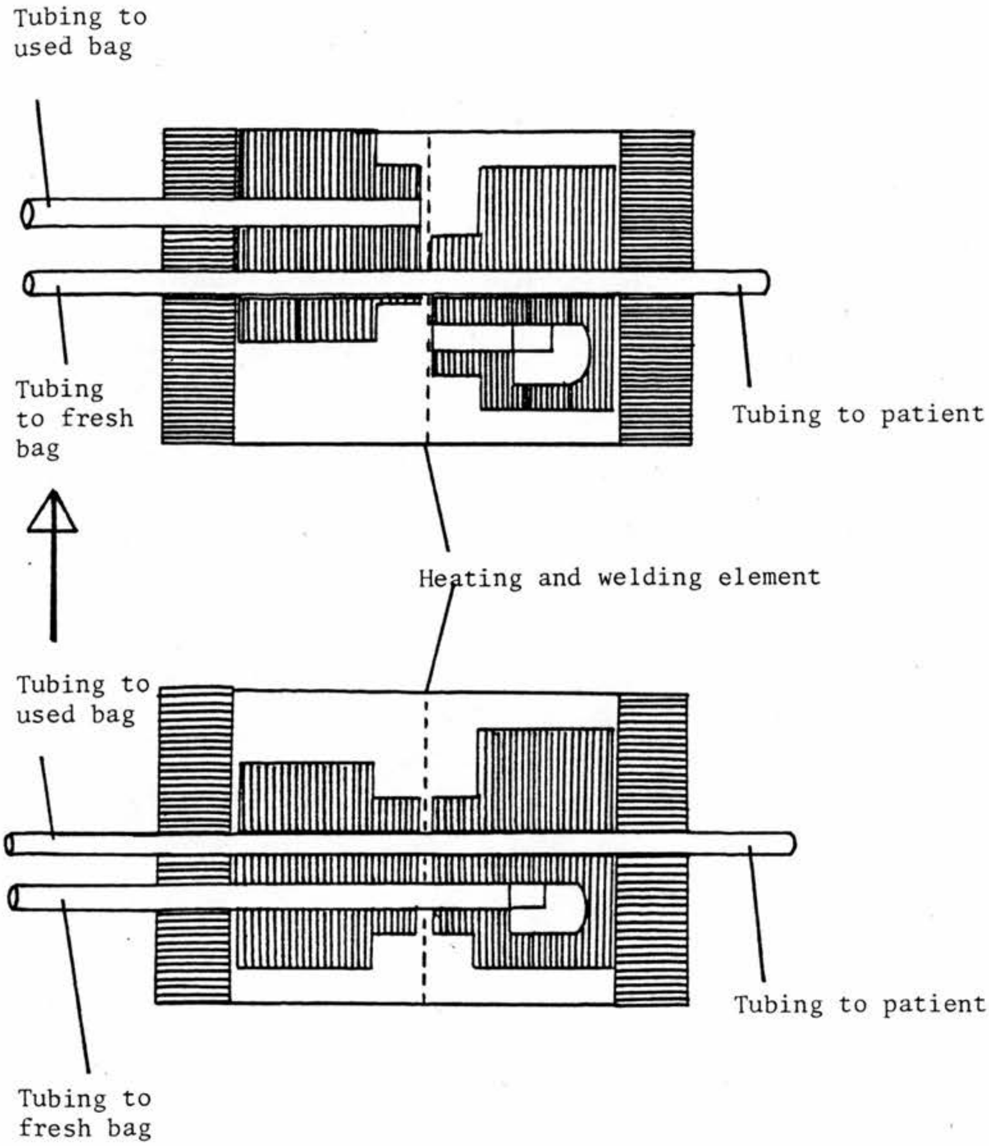

Figure E.2 The Sterile Weld Connector (adapted from Hamilton et al, 1983) the tubing of both the new and the used bags and simultaneously killing any micro-organisms present. The movable tubing carrier then shifts the melted ends and alligns the new bag and the administration tubing, welding them together. The weld is said to have at least 90% of the strength of the original tubing. Without supplying many details, the authors indicate that various tests of the device's bacteriological safety proved satisfactory. At present, the system is undergoing clinical trials. Provided it is reliable, safe and acceptably priced, it may well prove to be the answer to the CAPD maiden's prayer.

5. **Preventing Other Sources of Spread**

Considerable progress has therefore been made towards rendering the bag exchange free from the risk of contamination. It is clear, however, that in a proportion of episodes of peritonitis, the organism's portal of entry is elsewhere. Those which follow colonisation or infection of the exit site may be prevented by improvements in the design of the intraperitoneal catheter. Those which follow haematogenous spread from the mouth (viridans streptococci) or spread from the intestine or the female genital tract will be more difficult to prevent. At the Queen Elizabeth Hospital, we have encountered several cases of viridans streptococcal peritonitis in patients with oral lesions or who have had recent dental treatment (Kiddy et al, 1985). We have therefore stressed the importance of dental hygiene and recommended that CAPD patients undergoing dental treatment involving the gum should receive the same prophylactic antibiotics as are currently advocated for patients with cardiac valve lesions (Gruer et al, 1984b; Kiddy et al, 1985). Peritonitis as a complication of diverticulitis is particularly likely in elderly patients. For example, in one study of a CAPD population with an average age of 60 years, 9% of cases of peritonitis were attributed to diverticulitis (Slingeneyer and Mion, 1982). Some authors have therefore recommended that Barium studies should be carried out before starting CAPD: the presence of severe diverticular disease could weigh against accepting the patient for CAPD (Wu et al, 1983). A less problematic approach is to encourage all CAPD patients to take a high residue diet with the aim of avoiding constipation (Wu, 1983).

6. **Strengthening Intraperitoneal Defence**

A quite different preventive strategy has been suggested by studies of the natural defence mechanisms of the peritoneum. The reports of Slingeneyer and his colleagues showed that after 10-14 days of use, the upstream surface of in-line filters was contaminated wth micro-organisms in 25% of cases. Assuming that these organisms would reach the peritoneum in patients not using a filter, it appears that most organisms entering the peritoneum are eliminated by local defence mechanisms. Might, therefore, some patients develop peritonitis more often than others because their intraperitoneal defences are less effective? If this were so, could anything be done to enhance natural defences of the peritoneum?

One obvious approach is to use prophylactic antibiotics. However, it is virtually inevitable that the continuous use of antibiotics would lead to the selection of resistant bacteria. Furthermore, it is unlikely that ordinary doses of oral antibiotics could be relied upon to achieve adequate concentrations in the dialysate. In the only study of prophylactic antibiotics in CAPD so far published, Lowe and his colleagues (1980) studied 25 patients given cephalexin 500 mg twice daily for a total of 80 patient-months. This had no effect on the incidence of peritonitis. More recently, several groups of workers have taken a more fundamental approach, studying the behaviour of micro-organisms and the immune system in dialysate. The most interesting of their findings are discussed below.

Fresh dialysate does not support the growth of most bacteria causing CAPD peritonitis (Flournoy et al, 1983) and may be bactericidal for some strains (Diskin et al, 1983). However, both groups of workers found that after only a short period within the peritoneum, the dialysate sustained the growth of many species. The addition to fresh dialysate of serum or albumin, but not urea, had the same effect (Diskin et al, 1983). Diskin noted, however, that the dialysate effluent from four of twelve patients was bactericidal against the single coagulase-negative staphylococcus tested. The effluent from one patient was also bactericidal against a light inoculum of one of the two test strains of **E. coli.** This patient's effluent contained significantly greater quantities of IgA than effluent from others and was the only one in which complement C_3 was detected. Here, therefore, was preliminary evidence that the intraperitoneal environment might be more hostile to bacteria in some patients than others.

As discussed earlier, Vas and his colleagues (Vas et al, 1981; Duwe et al, 1981) showed that the phagocytosis of bacteria by polymorphonuclear leukocytes is markedly inhibited by fresh dialysate. This appears due to the low pH and high osmolality of the fresh dialysate. Phagocytosis is also compromised early in the dialysis dwell time because the numbers of both phagocytes and bacteria are low and hence the likelihood that the two will meet is small. In summary, therefore, these studies suggest that fresh dialysate suits neither the infective agent nor the host's defences. As time passes and dialysate-blood equilibration occurs, the intraperitoneal environment appears to become more favourable to both.

More recently, workers in Minnesota have studied the phagocytic activity of macrophages and polymorphs against strains of **Staph. epidermidis** and **E. coli** isolated from infected dialysate (Verbrugh et al, 1983; Keane et al, 1984). They found that, in the presence of normal pooled human serum, both cell types effectively phagocytosed **Staph. epidermidis** and **E. coli.** When heated serum was used, only **Staph. epidermidis** continued to be opsonised, indicating that the **E. coli** opsonin was a heat labile substance, probably complement. Phagocytes and bacteria were then incubated in dialysis effluent from 21 CAPD patients. Heat-stable opsonic activity against **Staph. epidermidis** was detected in five of the effluent samples but at titres about 100-fold lower than in serum. None of the dialysate samples opsonised **E. coli,** however. They found that there was a significant correlation between the opsonic activity of the dialysate against **Staph. epidermidis** and its IgA content. Subsequent studies have suggested that the principal opsonin for **Staph. epidermidis** in both serum and dialysate is an antibody against the peptidoglycan moiety of the staphylococcal cell wall (Keane and Peterson, 1984). These workers have also found that patients with low levels of heat stable opsonins in their dialysis effluent have a significantly higher incidence of peritonitis due to **Staph. epidermidis** than those with high levels. Since the opsonic activity of dialysate can be substantially increased by adding normal pooled human serum, they suggest that **Staph. epidermidis** peritonitis (and perhaps other forms) might be prevented by adding serum to fresh dialysate.

This interesting hypothesis remains to be tested. However, the technical advances discussed earlier in the chapter should lead to a reduction in the frequency of external contamination and hence to less staphylococcal peritonitis. Consequently, even if "passive immunisation of the peritoneum" is successful, its place in the prevention of peritonitis in the future may be limited.

At the time of completing this thesis (mid-1985), there is good reason to believe that improved techniques and a better understanding of intraperitoneal immunology will make CAPD peritonitis a much rarer condition. What remains in doubt is the long term durability of the peritoneal membrane, which is being required to perform a task for which it clearly was not designed. At present, the failure rate of CAPD remains high and the long term morbidity and mortality rates appear poorer for CAPD patients than for comparable patients on home haemodialysis (Coles, 1985). Is CAPD going to make a lasting contribution to the treatment of chronic renal failure, or is it going to be rendered obsolete by the arrival of fully portable haemodialysis units or some other, as yet unknown, approach? Time alone will tell.

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APPENDIX 1

EXAMINATION OF PERITONEAL FLUIDS FROM PATIENTS ON PERITONEAL DIALYSIS WITH SUSPECTED PERITONITIS PRESENTING OUTSIDE NORMAL LABORATORY HOURS - DISCUSSION PAPER

When CAPD patients present with suspected peritonitis outside normal laboratory hours, it is current practice for the duty renal houseman or registrar to call in the duty bacteriology technician to examine a sample of dialysis effluent. The technician will perform a white cell count, and gram stain, set up culture plates and place culture bottles in the incubator. At present, out-of-hours calls for PD fluid examinations number about ten per month, of which one to two per month are requested between midnight and 8.00 am. This represents 14% of all emergency out-of-hours bacteriology calls and one-third of after midnight calls for samples from Queen Elizabeth Hospital and Maternity Hospital patients.

In practice, the emergency examination of PD fluid rarely, if ever, alters the immediate management of the patient. The development of cloudy effluent is a clear indicator of the onset of peritonitis and the naked-eye appearance of the fluid correlates well with the white cell count. In less than ten per cent of cases of acute CAPD peritonitis are organisms seen on the gram stain and even then the picture can be misleading: in some instances, organisms seen on gram stain are not those which are ultimately cultured; in cases of peritonitis with mixed organisms, only one organism may be seen on gram stain, but more than one subsequently grown. Consequently, our current antibiotic policy should be adhered to, irrespective of the initial gram stain.

Thus, emergency PD cell counting and gram staining contribute little, if anything, to immediate patient management. It is essential, however, that the PD fluid inoculated into culture bottles be incubated immediately to permit early growth. On the other hand, PD fluid in universal containers can be refrigerated for 24 hours without invalidating the white cell count. Thus, a system which could guarantee that specimens were incubated and refrigerated in the hospital and then taken to the laboratory the following morning would not, as a rule, diminish the usefulness of the laboratory service but would obviate the need to call out the laboratory technician.

Exceptionally, patients are admitted with severe peritonitis and systemic disturbance. In these cases the laboratory technician should be called in to process the fluid. Thereafter, if concern remains, the renal medical staff should not hesitate to contact the medical bacteriologist on-call to discuss whether anything further can be done to hasten the diagnosis or improve treatment.

A routine out-of-hours system might be as follows. Specimens are taken and logged into a book in the CAPD room. The culture bottles are then taken by a member of the ward staff to the out-of-hours incubator. The universal container is placed in the ward refrigerator. It is then the responsibility of the CAPD nursing staff to ensure that the following morning the log book is checked and any samples taken promptly to the laboratory. The laboratory staff should be notified of the arrival of such specimens. The white cell count will be made and this and any provisional microscopy or culture results 'phoned to the duty renal registrar or the CAPD sister at the end of the morning.

Dr Laurence Gruer

APPENDIX 2

SUMMARY OF PROCEDURES FOR THE MICROBIOLOGICAL EXAMINATION OF DIALYSATE FROM CAPD PATIENTS WITH SUSPECTED PERITONITIS

A **Renal Unit Staff**

1) Normally, only cloudy dialysate should be sent.
2) Carefully wipe infection port of dialysate bag with a sterile alcohol swab.
3) Remove 80 mls of dialysate from dialysate bag via infection port using a sterile syringe and needle.
4) Change needle.
5) Inject 60 mls into a dialysate culture bottle and 20 mls into a sterile plastic universal cotainer.
6) If laboratory is open, dispatch properly labelled specimens immediately.
7) If laboratory closed, put culture bottle in the out-of-hours incubator and universal container in a refrigerator. Ensure that samples are sent as soon as the laboratory opens.

B **Laboratory Staff**

1) Normally, only cloudy dialysate samples should be processed.
2) Place dialysate culture bottle in standard incubator at 37°C.
3) Gently shake dialysate in universal container before removing a few drops to perform white cell count in

haemocytometer.

4) Centrifuge dialysate in universal container at 3,000 rpm for 15 minutes. Pour off all but one drop of supernatant. Prepare a smear for Gram stain and use remaining deposit to inoculate sheep blood and CLED agar for aerobic incubation.

5) Remove culture bottle from incubator after 18-24 hours. If growth is visible, perform a Gram stain and inoculate appropriate solid media. Report positive Gram stain findings to clinical microbiological staff.

6) If no growth is visible in culture bottle, inoculate sheep blood agar plates for aerobic and anaerobic incubation. Replace culture bottle in incubator. Examine bottles daily for signs of growth.

7) Identify isolates using normal methods.

8) Gram positive isolates should be initially tested for sensitivity to flucloxacillin, vancomycin, gentamicin and ampicillin. Gram negative isolates should be initially tested against gentamicin, ampicillin and cefuroxime.

9) Report identification and antibiotic sensitivity results to clinical microbiological staff. Record results of white cell count, culture and antibiotic sensitivity in CAPD peritonitis book.

10) All positive isolates should be inoculated onto agar slopes for preservation.

Dr Laurence Gruer

APPENDIX 3

DIAGNOSTIC BACTERIOLOGIQUE DES PERITONITES DE DPCA

CRITERES DE DIAGNOSTIC

Typiquement, une péritonite de DPCA débute par l'apparition d'un liquide de dialyse trouble. Secondairement, après quelques heures ou mêmes quelques jours, apparaissent les signes cliniques.

Le diagnostic se repose sur la mise en évidence dans le liquide de dialyse de plus de 100 polynucléaires neutrophiles par mm^3: un tel chiffre correspond à une turbidité de liquide et à une péritonite. La culture bactériologique est alors indispensable.

En revanche, il est désormais inutile d'analyser systématiquement au cours des visites le liquide de dialyse. A un liquide clair s'associe l'absence de péritonite, un faible nombre de polynucléaires et aucune valeur de toute culture bactérienne.

METHODES DE PRELEVEMENT POUR CYTOLOGIE ET CULTURE

Pour permettre le diagnostic bactériologique, le volume du liquide mis en culture doit être important, car le nombre de bactéries par millilitre de liquide de dialyse peut être faible. Le site d'injection du sac de liquide usé est nettoyé préalablement avec de l'alcool. Ensuite, 105 ml de liquide usé sont retirés avec une seringue stérile. 50 ml sont injectés avec une nouvelle aiguille dans chacun des deux flacons spéciaux (l'un avec un bouchon noir, l'autre vert), en les remplissant jusqu'à la ligne rouge. 5 ml sont mis dans un poudrier stérile pour la numération des globules blancs, au laboratoire de cytologie.

Les prélèvements sont adressés immédiatement aux laboratoires pendant leurs heures d'ouverture. Sinon, le poudrier est à garder au frigidaire, et les flacons de culture sont à mettre rapidement dans une étuve à 37°. Les prélèvements seront adressés secondairement aux laboratoires au moment de l'ouverture. Chaque prélèvement doit être daté et identifié par des étiquettes.

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APPENDIX 4

PUBLICATIONS BY THE AUTHOR RELATED TO THE CONTENT OF THE THESIS

SIR,—Dr Knight and his colleagues (Dec. 11, p. 1301) report success in treating peritonitis in patients on continuous ambulatory peritoneal dialysis (CAPD) with oral antibiotics. Cephradine was their drug of choice but erythromycin, co-trimoxazole and 'Augmentin' (amoxycillin and clavulanic acid) were also used. Cephradine has a narrower spectrum than that of cefuroxime, the first-choice treatment of CAPD peritonitis in several units in the U.K. Dr Gokal and others (Dec. 18, p. 1388) report a success rate of 58% in treating 136 episodes of CAPD peritonitis with cefuroxime. Our experience is similar. In the first half of 1982 we successfully treated 9 of 13 episodes of peritonitis with intraperitoneal cefuroxime alone (75 mg/l). During the next three months only 5 of 13 episodes were cured by cefuroxime, giving a success rate over nine months of 54%. Most of these later failures were due to strains of *Staphylococcus epidermidis (albus)* which had reduced sensitivity to cefuroxime on routine disc testing and which were only partly suppressed clinically, leading to a persistent or relapsing peritonitis. We therefore abandoned cefuroxime in favour of vancomycin, to which isolates of *Staph. epidermidis* have been consistently sensitive, and tobramycin, both given intraperitoneally.

We have since studied the sensitivity to cefuroxime and cephradine of forty-one distinct isolates of *Staph. epidermidis* from 29 episodes of CAPD peritonitis. The MIC_{50} (50% of isolates inhibited) for cefuroxime was 2 mg/l whilst that for cephradine was 8 mg/l. The MIC_{90} (90% of isolates inhibited) for both antibiotics was 32 mg/l. These high MICs indicate that oral cephradine would be no more successful in our situation than was cefuroxime. We suggest that the use of cephalosporins, including oral cephradine, in CAPD peritonitis is likely to be limited in the long term by the emergence of resistant *Staph. epidermidis.*

We have also treated CAPD peritonitis with oral augmentin, which we selected for its stability to β-lactamases produced by both gram-positive cocci and aerobic gram-negative bacilli. We treated ten patients, all of whom had early peritonitis without major systemic disturbance. Each patient received two augmentin tablets (amoxycillin 500 mg, clavulanic acid 250 mg) with food 30 min before each dialysis exchange. Only three of the ten patients responded satisfactorily. Of the remaining patients, two had an augmentin resistant *Klebsiella*; in two, nausea and vomiting led to discontinuation of the antibiotic; in three, the organism (*Staph. epidermidis*) was not eradicated despite in vitro sensitivity. Antibiotic concentrations in the dialysate effluent were measured in four patients. Amoxycillin levels were between 20 and 39 mg/l but clavulanic acid levels ranged from only 0·25 to 3 mg/l. The low concentration of clavulanic acid in the dialysate may well have played a part in the failure of augmentin to eradicate apparently sensitive organisms.

We thus consider oral cephradine and augmentin to be unsuitable for the routine treatment of CAPD peritonitis in our patients. Despite the potential advantages of oral therapy, we know of no oral antibiotic with a spectrum of activity and stability sufficient to warrant its use in preference to parenteral agents in this condition.

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Species identification and antibiotic sensitivity of coagulase-negative staphylococci from CAPD peritonitis

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Forty-three strains of coagulase-negative staphylococci were obtained from dialysis effluent during 41 episodes of CAPD peritonitis. Eighty per cent of these were found to be *Staphylococcus epidermidis* but several other species also occurred. A recurrent infection lasting 15 weeks was caused by *Staph. haemolyticus*. Multiple antibiotic resistance was found to be common. Of 13 antibiotics tested, only vancomycin was active against all strains although most strains were also sensitive to rifampicin, netilmicin and cefamandole. Vancomycin was chosen for the initial treatment of CAPD peritonitis caused by coagulase-negative staphylococci and eradicated the organism in 29 of 30 episodes.

Introduction

Peritonitis is the main serious complication of continuous ambulatory peritoneal dialysis (CAPD). All major published studies of CAPD peritonitis report that it is most commonly caused by coagulase-negative staphylococci (Rubin *et al.*, 1980; Chan *et al.*, 1981; Knight *et al.*, 1982; Gokal *et al.*, 1982; Vas, 1983). Such organisms are frequently resistant to many antibiotics, and may thus prove difficult to eradicate (Chan *et al.*, 1981; Vas *et al.*, 1981; Atkins *et al.*, 1981). During the first nine months of 1982, coagulase-negative staphylococci were responsible for 44% of the 45 episodes of CAPD peritonitis occurring at the Queen Elizabeth Hospital, Birmingham, including 10 of the 12 episodes which were not cured by the first course of antibiotics.

We therefore collected all coagulase-negative staphylococci isolated from the dialysis effluent of CAPD patients with peritonitis. Our aim was to characterize these organisms more precisely and to identify the antibiotics to which they were most consistently sensitive. We hoped this would permit us to select antibiotics which could be used with confidence to treat CAPD peritonitis caused by coagulase-negative staphylococci from the time of first presentation.

Materials and methods

Initial isolation and identification

A sample of 80 ml of dialysis effluent was collected aseptically from every CAPD

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patient presenting with acute peritonitis to the CAPD unit at the Queen Elizabeth Hospital, Birmingham. Twenty ml were placed in a sterile universal container. The remaining 60 ml were injected via a fresh sterile needle into a standard 100 ml medical flat bottle containing 20 ml of sterile nutrient broth (Oxoid No. 2) at four times normal strength, thereby diluting the broth to the correct concentration.

In the laboratory, a few drops of dialysate were removed from the universal container for a white cell count (Vas, 1983). Bacterial peritonitis was considered present if more than 100 neutrophil polymorphs/mm^3 were seen. The rest of the 20 ml was centrifuged and the deposit plated on to blood and CLED agar for aerobic incubation at 37°C for 24 h. The culture bottle was incubated aerobically at 37°C and subcultured on to blood agar after 24 h or if growth was detected visually at any time during the next nine days.

All isolates of Gram-positive cocci resembling staphylococci were purified on Columbia agar base (Oxoid Ltd) by twice plating out from a single colony. Isolates were subjected to the following primary identification tests: catalase, coagulase and oxidation or fermentation of glucose (Hugh & Leifson, 1953). All catalase-positive, coagulase-negative, fermentative isolates were then characterized further.

API Staphylococcus identification galleries (API, Montalieu, Vercien, France) were used according to the manufacturer's instructions. Tests included in the galleries were the fermentation of glucose, fructose, mannose, maltose, lactose, trehalose, mannitol, xylitol, melibiose, raffinose, xylose, saccharose, α-methyl glucoside and *N*-acetyl-glucosamine; the reduction of nitrate to nitrite; the production of acetyl-methyl-carbinol (V-P test); and the production of alkaline phosphatase, arginine hydrolase and urease. On the basis of the results each isolate was assigned a numerical profile which could then be used to identify the isolate from an index provided by the manufacturer and based on the classification of Kloos & Schleifer (1975).

Biotyping using conventional methods and phage-typing (de Saxe *et al.*, 1981) was carried out by the Central Public Health Laboratory (CPHL), Colindale, London. The tests used were the fermentation of fructose, maltose, lactose, trehalose, mannitol, xylitol, xylose, arabinose, ribose and sucrose; the reduction of nitrate to nitrite; and the production of acetoin and alkaline phosphatase. Each isolate was then assigned a biotype according to a modification of the Baird-Parker classification which could then be converted to the Kloos & Schleifer classification (Marples, 1981; Marples & Richardson, 1982).

Antibiotic sensitivity testing

Thirteen antibiotics with known anti-staphylococcal activity were tested. The minimum inhibitory concentration (MIC) of each antibiotic for each isolate was found by a standard agar plate dilution method (Waterworth, 1978) with Iso-Sensitest agar (Oxoid, Ltd). Control strains of coagulase-negative staphylococci were provided by the Antibiotic Research Laboratory, Dudley Road Hospital, Birmingham and were included on each plate. All MICs were determined after 24 h incubation except for flucloxacillin, cefuroxime and cefamandole where the determination was made at 48 h.

A short antibiogram was obtained for each isolate using five antibiotics (gentamicin, erythromycin, clindamycin, flucloxacillin and fusidic acid) to each of which resistance was common and apparently independent. The production of β-lactamase was detected by the method of Park, Lopez & Cook (1978).

Results

A total of 61 isolates of coagulase-negative staphylococci were obtained from 52 specimens of dialysis effluent during the period 1 May 1982 to 30 April 1983. These specimens were collected during 41 episodes of acute peritonitis in 25 patients. A coagulase-negative staphylococci was twice cultured concurrently with an acinetobacter, once with a *Staph. aureus* and once with an α-haemolytic streptococcus. On seven occasions, two or three colonial types of coagulase-negative staphylococci were obtained from a single specimen. On five of these occasions further characterization showed that they were all colonial variants of the same strain, but on two occasions the isolates had different biotypes and antibiograms.

Table I. Speciation of 43 distinct strains of coagulase-negative staphylococci from patients with CAPD peritonitis

Organism	Method of biotyping API	Conventional*
Staph. epidermidis	36	34
Staph. haemolyticus	2	2
Staph. warneri	1	2
Staph. cohnii	1	1
Staph. capitis	1	0
Staph. simulans	0	2
Staph. hominis	1	2
Untypeable	1	0

*Tests carried out by Central Public Health Laboratory, Colindale.

Identification

After considering the source, biotype, phage type and antibiotic sensitivity of each of the 61 isolates, we were able to distinguish only 43 strains. These are classified according to species in Table I which shows that most were *Staph. epidermidis*. There was close agreement between API and CPHL biotyping as to which strains were *Staph. epidermidis* but several of the other strains were speciated differently by the two methods.

The same strain was isolated more than once from each of nine patients. In five, all the isolates were cultured during the initial course of antibiotics and were not re-isolated thereafter. In three, the same strain was re-isolated between one and three weeks after the first course of treatment but did not recur after the second course. In one patient the same strain of *Staph. haemolyticus* was isolated from the dialysate on four different occasions over a period of 15 weeks. On each of these occasions the patient had peritonitis and no other organism was isolated.

During the 12 months of the study, four patients had two separate episodes of

Table II. Percentage of isolates of coagulase-negative staphylococci resistant to five antibiotics in various studies

Antibiotic	CAPD peritonitis isolates ($n=43$)	Richardson & Marples (1982) ($n=532$)	Marsik & Brake (1982) ($n=203$)	Smith *et al.* (1982) ($n=191$)	Gemmell & Dawson (1982) ($n=100$)
Gentamicin	40	27	8	24	0
Erythromycin	42	31	41	43	—
Clindamycin	12	—	36	36	0
Methicillin	35	37	66	39	0
Fusidic acid	9	25	—	—	0

peritonitis caused by different strains of coagulase-negative staphylococci, three patients had three and two had four.

Phage typing

Only 26 of the 59 isolates tested showed lysis by one or more phages and lysis was often weak. On two occasions, phage typing clearly differentiated isolates from the same patient which had identical biotypes and antibiograms. Phage typing also sometimes confirmed that isolates cultured on different occasions from the same patient were identical.

MIC_{50} and MIC_{90}

All but six of the 43 distinct strains produced β-lactamase. The MICs of each of the 13 antibiotics for 50% and 90% of the strains are shown in Table III. Also included in the Table are the antibiotic concentrations which can be readily but safely achieved in dialysis fluid and blood. Only six of the 13 antibiotics—vancomycin, rifampicin, netilmicin, cefamandole, fusidic acid and clindamycin achieved an adequately low MIC_{90}. All strains were sensitive to 1 or 2 mg/l of vancomycin and only one strain was resistant to rifampicin. All but two strains were sensitive to netilmicin and cefamandole at 2 and 4 mg/l, respectively, but the MICs of both these antibiotics varied between strains by a factor of up to 64 suggesting that strains with greater resistance might readily emerge. There were few strains resistant to clindamycin (all >32 mg/l) and four to fusidic acid (>8 mg/l).

We concluded that vancomycin appeared to have the most consistent activity of all the antibiotics tested. Rifampicin, netilmicin and cefamandole also seemed worthy of further consideration for clinical use.

Antibiograms

Sixteen of the 61 isolates tested were sensitive to all five antibiotics but each of the other 45 isolates was resistant to between one and four. Table II shows the percentages of strains which were resistant to each of the five antibiotics compared with those from four other recent studies of coagulase-negative staphylococci isolated from a variety of clinical specimens.

There were 14 different patterns of resistance to the five antibiotics among our isolates, several patterns being unique to isolates from a single patient. On all but one occasion, isolates with identical phage types also had identical antibiograms.

Table III. MIC_{50} and MIC_{90} of 13 antibiotics for strains of coagulase-negative staphylococci from patients with CAPD peritonitis compared with achievable dialysate and blood levels

	No. of strains tested	MIC_{50} (mg/l)	MIC_{90} (mg/l)	Dialysate* (mg/l)	Blood† (mg/l)
Vancomycin	41	2	2	15	20
Rifampicin	41	0·004	0·008	—	5‡
Netilmicin	41	0·125	1	6	4
Cefamandole	39	1	4	30	10
Fusidic acid	41	0·125	2	25	20
Clindamycin	42	0·06	0·125	25	5
Flucloxacillin	43	2	>32	50	10
Cephradine	35	16	32	—	10‡
Cefuroxime	35	16	>32	30	10
Erythromycin	42	0·125	>32	—	1·5‡
Gentamicin	41	0·125	16	4	4
Tobramycin	35	0·125	>16	4	4
Trimethoprim	35	>16	>16	—	3‡

*Approximate mean inter-dose level following standard intra-peritoneal dose (Oreopoulos *et al.*, 1981).

†Approximate mean inter-dose level following standard intravenous dose (or oral dose where marked) suitable for patient with severe renal impairment (Garrod, Lambert & O'Grady, 1981).

‡Given orally.

Conversely, only twice did an isolate have a different phage type but the same antibiogram. Thus, phage typing and the antibiogram had similar usefulness.

Discussion

The analyses of the bacteria causing CAPD peritonitis which have appeared to-date do not distinguish between *Staph. epidermidis* and other coagulase-negative staphylococci. In therapeutic terms this probably does not matter, but it means that certain epidemiological features of coagulase-negative staphylococci peritonitis have been obscured. Studies on normal human skin have shown that *Staph. epidermidis* comprise only 23% of the coagulase-negative staphylococci on the skin (Kloos & Schliefer, 1975). In contrast, studies of clinical isolates of coagulase-negative staphylococci show that from 63 to 81% are *Staph. epidermidis* (Marsik & Brake, 1982; Gemmell & Dawson, 1982; Sewell *et al.*, 1982) whilst as many as 93% of clinically significant coagulase-negative staphylococci infections may be caused by *Staph. epidermidis* (Sewell *et al.*, 1982). The present study of 43 distinct strains of coagulase-negative staphylococci, all of which were thought to be clinically significant, showed that about 80% were *Staph. epidermidis*. Thus, the apparently greater pathogenicity of *Staph. epidermidis sensu stricto* compared with other coagulase-negative staphylococci includes a greater ability to cause CAPD peritonitis. Nevertheless, the infection can also be caused by other coagulase-negative staphylococci. Most notably, *Staph. haemolyticus* was responsible for a recurrent infection lasting 15 weeks.

We found that biotyping was helpful in determining which isolates represented persisting and which fresh infection. As other authors have found, the API Staph system gave results which correlated well with those of conventional methods, yielding numerical profiles which could be readily compared (Marples & Richardson, 1982; Gemmell & Dawson, 1982; Ellner & Myrick, 1982). Further differentiation of some strains was made possible by phage typing or antibiotic sensitivity testing, but both approaches had disadvantages. The phage-typing system could type only 50% of isolates and extensive antibiotic sensitivity testing is too laborious for routine, clinical use. The short antibiogram, on the other hand, proved capable of differentiating some strains, as well as providing clinically useful information.

Resistance to flucloxacillin, cefuroxime, cephradine, gentamicin, tobramycin, trimethoprim and erythromycin was sufficiently frequent among our isolates coagulase-negative staphylococci to make these agents unsuitable for routine use. Although apparently not universal, resistance to these and other antibiotics is widespread (Table II) and may be increasing. Richardson & Marples (1982) have noted that the proportion of gentamicin-resistant strains of coagulase-negative staphylococci has risen from 7% in 1976–77 to 33% in 1980.

Cefamandole and netilmicin were both notably more active than the other cephalosporins and aminoglycosides we tested, a feature recently noted elsewhere (Smith *et al.*, 1982; D. C. E. Speller, personal communication). However, their MICs varied greatly from strain to strain suggesting that a progressive decrease in the sensitivity of coagulase-negative staphylococci to both antibiotics might occur if they were used extensively. Despite the excellent activity of rifampicin against all but one strain we felt that its special role in treatment of tuberculosis precluded its routine use in CAPD peritonitis.

Vancomycin-resistant strains of coagulase-negative staphylococci are rarely found at present (Vas *et al.*, 1981; Atkins *et al.*, 1981; Smith *et al.*, 1982) and did not occur in our study. Vancomycin therefore emerged as the best of the antibiotics tested *in vitro* and was thus chosen for the initial treatment of coagulase-negative staphylococci peritonitis in our patients. From October 1982 to July 1983, we treated 30 episodes of coagulase-negative staphylococci peritonitis with intraperitoneal vancomycin for 10–12 days. In only one case was the organism not eradicated and no adverse effects of the antibiotic were observed. We therefore conclude that vancomycin is the best antibiotic currently available for the treatment of CAPD peritonitis caused by coagulase-negative staphylococci.

Acknowledgements

We thank Dr Richard Marples, Central Public Health Laboratory, Colindale, London, for kindly biotyping and phage-typing our isolates, and the staff of the Renal Unit, Queen Elizabeth Hospital, Birmingham for their co-operation.

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of these compounds on chlamydial DNA synthesis.

MICs and MLCs of ciprofloxacin and norfloxacin already reported in conventional tests (Meier-Ewert *et al.*, 1983, 1984; Heesen & Muytjens, 1984; Ridgway *et al.*, 1984) are approximately four-fold lower than our figures. Our results show that ofloxacin is more active than other quinoline carboxylic acids tested *in vitro* against *Chlam. trachomatis* to date. They also suggest that IF stains may be more sensitive (and hence give slightly higher MICs and MLCs) than iodine or Giemsa when antimicrobial agents are assessed *in vitro* for their antichlamydial activity.

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Vancomycin in the treatment of CAPD peritonitis

Sir,

Dr Gruer and his colleagues (Gruer, Bartlett & Ayliffe, 1984) conclude that vancomycin should be the drug of choice for the initial treatment of CAPD peritonitis caused by coagulase-negative staphylococci. May we make two brief comments?

An episode of CAPD peritonitis requires empirical treatment until the causative organism is known – this may be as soon as 24 h from the onset of symptoms, but is usually 48 h or longer, with antibacterial sensitivities not available until a day later. In most of the studies cited by Gruer Gram-negative organisms have accounted for at least one third of the episodes. Initial empirical treatment must therefore take this into account, and vancomycin alone would be inappropriate.

Secondly, the source of infection is, with rare exceptions, the skin, and incorrect or careless handling of the apparatus the cause of peritonitis. As the addition of an antibiotic to the dialysis bag provides yet another opportunity for contamination of the system, we investigated the efficacy of empirical oral treatment (Knight *et al.*, 1982). We chose cephradine for this purpose, in view of its reasonably wide Gram-negative and Gram-positive spectrum; oral cephradine is now used here for the first line treatment of CAPD peritonitis. The majority of strains of coagulase-negative staphylococci continue to be sensitive to cephradine *in vitro* (50 of the 72 isolates since January 1983). Episodes which fail to respond require different treatment when the organism is known, and we agree that vancomycin is a useful agent for treating refractory episodes caused by coagulase-negative staphylococci.

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This letter has been shown to Dr Gruer whose reply follows

Sir,

The aim of our paper was not to describe our policy for the initial treatment of CAPD peritonitis: this will be covered in a future publication. Our aim was to examine the antibiotic sensitivities of coagulase-negative staphylococci causing CAPD peritonitis. In our patients, these were the organisms most frequently isolated, most often resistant to many antibiotics and hence most difficult to treat. Deciding on the best antibiotic for treating coagulase-negative staphylococcal peritonitis thus seemed an essential first step in formulating an initial treatment policy. Vancomycin emerged as the most reliable antibiotic (0% resistance). On the other hand, more than half the strains we tested were resistant to cefuroxime (previously our antibiotic of choice) and cephradine, making them unsuitable first line agents. Resistance to cephradine in Portsmouth is, at 30%, lower than in Birmingham but still seems an unsatisfactory level for a first-line antibiotic.

Further study of other organisms isolated from infected dialysate showed that satisfactory initial cover could not be provided by a single antibiotic. Vancomycin was the best agent for Gram-positive and an aminoglycoside for Gram-negative isolates. Thus, for the past two years, the renal unit at the Queen Elizabeth Hospital, Birmingham has used intraperitoneal vancomycin and gentamicin for initial treatment, dropping the inappropriate agent or, very rarely, changing to another antibiotic when sensitivities are known.

I believe that Maskell and Crump's advocacy of oral antibiotics is ill-founded. Unless very advanced, CAPD peritonitis is a localised infection and bacteraemia is extremely rare. It seems inappropriate to rely on unpredictable enteral absorption leading to usually rather low intraperitoneal antibiotic concentrations. Injection of antibiotics into the fresh dialysate bag via the injection port delivers high concentrations of antibiotic immediately to the site of infection. I have never encountered secondary CAPD peritonitis due to the use of intraperitoneal antibiotics and am unaware of any published evidence for this.

To make treatment easier to carry out at home and to reduce the risk of accumulation of potentially ototoxic antibiotics, we now add 100 mg vancomycin and/or 40 mg gentamicin to the overnight bag only, for ten days. This ensures a dwell-time of at least six hours and allows some peritoneal clearance of antibiotics during the rest of the day. This approach has proved surprisingly successful. Of the first 100 episodes thus treated, 88 were cured by the ten day course and four by an extended course of vancomycin. Other antibiotics were required in six episodes, all for gentamicin-resistant Gram-negative organisms. In only two cases did the catheter have to be temporarily removed. Only eight patients had to be hospitalised for more than one night because of their infection. Serum antibiotic levels were satisfactory with maximum serum concentrations of 12 mg/l and 3 mg/l for vancomycin and gentamicin respectively. No clinical side effects of the treatment were observed. No vancomycin-resistant Gram-positive organisms have been encountered and refractory coagulase-negative staphylococcal peritonitis has ceased to be a major problem.

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Susceptibility of *Clostridium difficile* strains to new antibiotics: quinolones, efrotomycin, teicoplanin and imipenem

Sir,

The recent influx of new antibacterial agents, many of which appear in high concentration in faeces promoted us to examine 23 epidemiologically unrelated strains of *Clostridium difficile* isolated from different wards and the community in Cambridge. Cultures were grown in brain heart infusion broth (incubated anaerobically for 48 h), then an inoculum was made by diluting each tenfold with the same broth and applying approx 0·002 ml to plates containing Iso Sensitest agar with 5% lysed horse blood and dilutions of the antibiotics. The inocula contained *ca* 10^5 cells, and the plates were read after 24 h incubation in an anaerobic cabinet (Whitley).

The agents which were kindly donated by the makers were: ofloxacin (Hoescht), pefloxacin (May & Baker), norfloxacin (Merck, Sharpe & Dohme), ciprofloxacin (Bayer), and enoxacin (Warner Lambert); other agents included efrotomycin, imipenem (Merck, Sharpe and Dohme), and teicoplanin (Merrell). Vancomycin was used as a reference drug.

The results are shown in Table I; excluding those for norfloxacin (64 mg/l), enoxacin (> 32 mg/l) and ofloxacin (8 mg/l) for which all the strains gave the identical values given in brackets. Several points of interest emerge. Efrotomycin and teicoplanin are obviously

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Disinfection of hands and tubing of CAPD patients

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Summary: During a 3 month study the effectiveness of two methods of handwashing was assessed in a group of 31 patients undergoing continuous ambulatory peritoneal dialysis. A defined, double rinse with alcohol, prior to bag exchange, was found to be more convenient and significantly more effective than povidone-iodine alone or povidone-iodine followed by alcohol. Spraying the tubing around the bag connector with 70 per cent ethanol reduced the numbers of adherent skin organisms so reducing the likelihood of bacteria being drawn into the dialysate. Although there was no difference in the overall incidence of peritonitis in the two groups of patients studied, there was an unexpected drop in the incidence of peritonitis caused by coagulase-negative skin staphylococci. This was attributed to an overall awareness of the importance of handwashing and aseptic procedures during bag exchange. Monitoring the bacteriology of the catheter exit site may give some prior indication as to the likelihood of subsequent peritonitis especially with *Staphylococcus aureus* and Gram-negative bacilli.

Introduction

Peritonitis is the main reason for failure of continuous ambulatory peritoneal dialysis (CAPD) (Gokal *et al.*, 1982). The bacteria causing peritonitis are commonly resident skin flora, e.g. coagulase-negative staphylococci, but may include transient Gram-negative bacilli (Editorial, 1982). The organisms may enter the system via either of the two connectors between the dialysate bag and catheter, or along the track of the catheter from the abdominal wall (Parsons *et al.*, 1983). Infection may arise from the patient's hands or the skin of the abdomen adjacent to the catheter exit site. Patients are generally instructed in techniques of handwashing and care of the exit site. A variety of disinfectants are used and include povidone-iodine, chlorhexidine and alcohol. Although the effects of these agents have been studied on the hands of staff (Ayliffe, 1980), they have not been evaluated on the resident flora of patients' hands.

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In this study, two methods of disinfection of the hands are compared and the incidence of peritonitis recorded. Decontamination of the connector and associated tubing and the skin adjacent to the catheter exit were also investigated.

Materials and methods

The study took place during a 3 month period between February and May 1983. The 31 patients practising CAPD at the Queen Elizabeth Hospital, Birmingham, were each randomly allocated to one of two groups. Group A contained 16 patients and Group B 15. The groups were found to be matched in terms of age, sex, time on CAPD, previous episodes of peritonitis and proportions of diabetics to non-diabetics. All patients used the 'Travenol IIR' system, and carried out three or four exchanges per 24h.

Skin disinfection before bag exchange

Hands were disinfected before preparation of the surface, administration set and bag, and immediately prior to exchange. Group A patients continued to use the existing method consisting of a thorough handwash with povidone-iodine detergent ('Betadine' surgical scrub) followed by an application of 5ml of 70 per cent ethanol containing 1 per cent glycerol as an emollient. Group B patients applied 5ml of 70 per cent ethanol and 1 per cent glycerol to the cupped hands and gently rubbed until dry. The process was then repeated. A defined procedure was taught to ensure all surfaces of hands were covered (Ayliffe, Babb and Quoraishi, 1978). Group A used a non-medicated soap and Group B 4 per cent chlorhexidine-detergent ('Hibiscrub') for general handwashing.

Group A cleaned the catheter exit site with povidone-iodine detergent and Group B with chlorhexidine-detergent. Both groups wore masks during the exchange and Group B also sprayed the outer surface of the bag connector and adjacent tubing with 70 per cent ethanol.

Bacteriological sampling

Samples were taken from the hands, the catheter exit site and the administration tubing at monthly intervals where possible, or in most cases two to four times during the study.

Samples were taken from the hands before and after disinfection using two methods.

(1) Broth sampling. The tips of the fingers and thumb of one hand were gently kneaded for 1 min on the bottom of a Petri dish containing 10 ml of recovery medium. The recovery medium contained nutrient broth (No. 2, Oxoid Ltd, Basingstoke) with 0·75 per cent lecithin-tween mixture and 1 per cent sodium thiosulphate to neutralize residual povidone-iodine or chlorhexidine. Neat and 10-fold dilutions were then drop-pipetted on to the surface of blood and

phenolphthalein disodium phosphate (PPD) agar plates. The agar (Oxoid No. 2) was enriched with 1 per cent horse serum.

(2) Finger streaks. This method was used to estimate the number of bacteria readily detachable from each finger tip. The fingers and thumb of the other hand were streaked across the surface of a nutrient agar plate (PPD).

The skin of the abdominal wall immediately adjacent to the exit site was sampled using (1) a contact plate ($25\,cm^2$) containing either PPD or blood agar, (2) a swab moistened in Ringer's solution which was then plated directly on to blood and PPD agar.

Swabs moistened in Ringer's solution were used to sample both the bag and peritoneal catheter connectors and also the tubing for 4–5 cm on each side of the connectors. A further sample was taken from Group B patients from the bag connector and adjacent tubing following disinfection with alcohol.

Swabs moistened in Ringer's solution were taken from the anterior nares and cultured immediately on PPD agar.

In the event of a CAPD patient presenting with a bag containing turbid fluid which was found to have more than 100 leucocytes/mm^3, the dialysate was cultured as follows: 20 ml were centrifuged and the deposit plated out on blood and cystine lactose electrolyte deficient (CLED) agar plates; 60 ml were added to a 100 ml medical flat bottle containing 20 ml of sterile nutrient broth (Oxoid No. 2) at four-times normal strength, the addition of the dialysate thereby diluting the broth to the correct concentration.

All plates and broth cultures were incubated aerobically at 37°C for 18 h. Plates were re-incubated for 24 h at room temperature to assist with identification of coagulase-negative staphylococci and counts were made where appropriate. Strains were identified by conventional tests and the API system was used for all Gram-negative bacilli and selected coagulase-negative staphylococci from patients with peritonitis.

Results

In Group A, the treatment of one patient was changed to haemodialysis before he could be sampled, and another was unable to attend the sampling clinic. The 14 remaining patients in Group A were sampled on a total of 36 occasions. The 15 patients in Group B were sampled on 49 occasions.

The number of resident skin bacteria recoverable from the fingers by the broth sampling method before skin disinfection varied considerably from patient-to-patient (range: $1{\cdot}8 \times 10^2$–$7{\cdot}2 \times 10^6$). The median counts in the two groups were, however, very similar ($1{\cdot}6 \times 10^4$ and $3{\cdot}3 \times 10^4$).

Using the broth sampling technique, there was an increase in the mean bacterial counts following the use of povidone-iodine alone and povidone-iodine followed by alcohol. These increases were 107 per cent and 51 per cent respectively. There was, however, a mean bacterial count reduction of 69 per cent in the defined double alcohol treatment group. Thus, the defined double alcohol treatment resulted in a significantly greater reduction than either povidone-iodine alone or povidone-iodine plus alcohol ($P < 0{\cdot}001$). On 16 of 29 occasions (55 per cent) more resident flora were recovered after than before washing with povidone-iodine alone, and 12 of 36 (33 per cent) occasions after povidone-iodine plus alcohol. On five occasions the bacterial count after povidone-iodine plus alcohol increased more than five-fold. On only five of the 47 occasions (11 per cent) did the bacterial count rise following the defined double alcohol wash, the greatest increase being 3·6-fold.

Table I shows that with the finger-streak sampling method lower bacterial counts were obtained following the double alcohol treatment than with the other products. Significantly lower counts of resident flora were also obtained from the thumb, middle and ring fingers after using a defined alcohol wash procedure.

Organisms isolated from the hands were mainly coagulase-negative staphylococci. *Staphylococcus aureus* was recovered from the hands before disinfection in five Group A patients on a total of eight occasions and from seven Group B patients on 11 occasions. Following disinfection, *Staph. aureus* could still be isolated from four of the five Group A patients and two of the Group B patients. These differences were not statistically significant. The following Gram-negative bacilli were recovered from 11 of the 83 samples (13 per cent) before disinfection, but none of the samples after disinfection: *Acinetobacter* spp., eight samples from six patients; *Proteus mirabilis* from two patients and *Escherichia coli* from one patient. On only three occasions did the number of Gram-negative bacilli recovered from a broth sample exceed 100. A few colonies of *Streptococcus viridans* were recovered from one of the 83 pre-disinfection samples.

Table 1. *Effectiveness of hand disinfection prior to bag exchange: finger-streak sampling*

	No. of patients sampled (fingers)	Range of bacterial counts	Percentage of fingers
After two applications		No growth	60·5
of alcohol	43	1–10	33·5
(Group B)	(215)	11+	6·0
		No growth	39·3
After povidone-iodine	29	1–10	28·3
Group A	(145)	11+	32·4
After povidone-iodine		No growth	45·2
and alcohol	31	1–10	29·0
(Group A)	(155)	11+	25·8

Contact plate sampling of the exit site gave very similar counts in both the chlorhexidine and the povidone-iodine treated groups. Counts ranged from less than 10 colonies to confluent growth, but in both groups there was a moderate to heavy growth in about 70 per cent of samples and a very heavy or confluent growth in 20 per cent. Exit site samples from three patients in Group A and four patients in Group B showed *Staph. aureus*. *Staphylococcus aureus* was also grown from the hands before disinfection in all of these patients. *Acinetobacter* spp. were isolated from the exit site of four of the six patients from whose hands they had been recovered. *Proteus mirabilis* was cultured from the exit site of one patient.

The results of sampling the administration tubing before and after spraying with 70 per cent ethanol are shown in Table II. This shows that there was more contamination of the tubing around the peritoneal catheter, which lies close to the abdominal wall, than around the bag connector. Spraying the tubing around the bag connector with alcohol led to a large reduction in counts, with 82 per cent of samples taken after disinfection showing no growth.

Table II. *Contamination of the administration tubing before and after disinfection with 70% alcohol*

	Pre-disinfecion samples (%)		Post-disinfection samples (%)
Bacterial counts in range	Peritoneal catheter connector	Bag connector	Bag connector
0	14	26	82
1–10	37	57	16
11–100	38	17	2
100+	11	0	0
Sample number	84	35	49

Over the 3 months before the start of the study (period 1) there were 23 episodes of peritonitis during 94 patient-months of CAPD (one episode per 4·1 patient-months). Over the 3 months after the start of the study (period 2) there were 16 episodes during 106·5 patient-months (one episode per 6·7 patient-months). Seven of these 16 episodes occurred in six Group A patients, and nine in six Group B patients. The organisms isolated during the two periods are shown in Table III. This shows that the number of episodes of peritonitis caused by coagulase-negative staphylococci fell substantially during period 2, i.e. 11 of 27 patients during period 1 and in only three of 29 patients during period 2, a significant difference ($P < 0{\cdot}02$). The proportion of patients developing peritonitis caused by other organisms did not change significantly.

Table III. *Organisms causing peritonitis in CAPD patients*

Organism	Number of isolates in Period 1 (27 patients)	Number of isolates in Period 2 (study period) (29 patients)
Coagulase-negative staphylococci	15	2
Coagulase-negative staphylococci		
with *Staph. aureus*	1	0
with *Str. viridans*	0	1
with diphtheroids	1	0
with Gram-negative bacilli	1	0
Diphtheroids	0	1
Staph. aureus	0	3
Str. viridans	0	4
Acinetobacter spp.	2	1
Other Gram-negative bacilli	1	2
Yeasts	0	1
Unknown	2	1
Total	23	16

Discussion

Most evaluations of ward handwashing techniques have been concerned with the removal of potentially pathogenic bacteria, e.g. *Staph. aureus* and *Klebsiella* spp, which are transiently found on the hands of nurses and medical staff. As CAPD peritonitis is often caused by coagulase-negative staphylococci, and as it is the patient himself who usually carries out the bag exchanges, it is important to know how effective are the skin disinfection procedures on the resident as well as the transient skin flora.

Our study has shown that the povidone-iodine detergent, as used by our patients, is often totally ineffective in reducing the resident skin flora on the fingers. Possibly this is due to inadequate contact time. The mean count following povidone-iodine detergent showed an increase in counts on more than half the occasions. This increase is probably the result of the detergent bringing to the surface bacteria lodging in pores and skin creases. The use of 70 per cent ethanol after povidone-iodine slightly improved disinfection, but in many instances the counts were still higher than before disinfection. The defined double alcohol wash was significantly more effective, with a mean count reduction of 69 per cent. Nevertheless, on a few occasions counts were still higher after the alcohol wash than before.

There are probably two main reasons for the greater effectiveness of the defined double alcohol wash. First, 70 per cent alcohol kills bacteria more rapidly than povidone-iodine. Secondly, the defined wash means that there is less chance that any part of the fingers will avoid disinfection. The finger-streak samples showed that the difference between the two methods was most pronounced on the thumb, middle and ring fingers. Previous work has shown that these areas are often missed during handwashing (Taylor, 1978). The alcohol wash was generally preferred by patients, and it could be carried out without using a handwash-basin making it very suitable for travellers and holiday makers. Once learned, the technique was quicker than using povidone-iodine detergent. The alcohol, being almost colourless, did not stain clothes or jewellery and, with added glycerol, was found by some patients to be gentler to the skin than povidone-iodine. The use of chlorhexidine-detergent, instead of non-medicated soap, for routine hand treatment showed no obvious benefit.

Despite the superiority of the double alcohol wash over povidone-iodine and a single application of alcohol, we were unable to show any difference between the two groups in the incidence of peritonitis during the short period of the study. We did, however, observe an unexpected reduction in the overall incidence of peritonitis caused by coagulase-negative staphylococci, with three episodes during the study as against 18 episodes during the same period before the study. Although Group A patients were not specifically instructed in handwash techniques during the study they inevitably became aware that this was what we were studying. Consequently, patients in both groups may well have paid more attention to their exchanges with less contamination of the bag connector as a result. Indeed, recent connector design should ensure that the bag exchange can be carried out aseptically even with dirty hands, provided the technique is meticulous.

Each of the three episodes of *Staph. aureus* peritonitis was caused by organisms identical to isolates previously cultured from the patient's nose, hands and exit site. Those patients who had *Staph. aureus* on the hands but not on the exit site did not develop *Staph. aureus* peritonitis during the study. This perhaps favours the exit site as a focus of colonization from which spread to the peritoneum later occurred. Similarly, acinetobacter peritonitis occurred in two of the four patients with the organism on the exit site as well as on the hands. A similar strain was found on the face-flannel of one of these patients. Colonization of the exit site by potential pathogens occurred despite reported daily cleansing of the exit site with either povidone-iodine or chlorhexidine detergent. Both these agents thus seem inadequate for the purpose. It may be that the detergent has a damaging effect on the skin which favours colonization.

Our study showed that *Str. viridans* are almost never found on the hands or exit site of CAPD patients. A much more likely route into the peritoneum is from the mouth via the bloodstream. This hypothesis is strengthened by the fact that two of the four episodes of *Str. viridans* peritonitis during the study period occurred in the only splenectomized patient in the group. While further work is required to confirm this hypothesis, we believe the evidence is sufficient to recommend prompt attention to gingivitis and prophylactic erythromycin when traumatic dental treatment is being undertaken; CAPD patients should also be advised to use a soft toothbrush.

Our failure to isolate oral flora from the skin or tubing indicates that direct spread from the mouth is an unlikely route of spread. We have, therefore, dispensed with the mask, further simplifying the bag changing routine and increasing its social acceptability.

If the incidence of CAPD peritonitis is to be reduced, the bag exchange must be made a more foolproof procedure. Disinfection of the connection site between the administration set and the bag using a povidone-iodine spray (Parsons *et al.*, 1983) or flushing with a hypochlorite solution has been shown to be effective (Maiorca *et al.*, 1983).

Nevertheless, an effective aseptic procedure would be preferable and CAPD unit staff should aim constantly to encourage a meticulous exchange technique. A defined double alcohol wash may be the best available means of hand disinfection but the importance of hand disinfection *per se* should not be overvalued.

We wish to thank Sister J. Curley and the staff and patients of the CAPD Unit at the Queen Elizabeth Hospital, Birmingham, for their enthusiastic co-operation.

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Letters to the Editor

Sir,

CAPD Peritonitis

In their interesting leading article, Spencer & Fenton (1984) referred to several unsatisfactory culture techniques and suggested that the pour-plate technique used in their laboratory (Fenton, 1982) is the method of choice. This requires that the specimen must be handled from the outset in the laboratory by technical staff. We prefer a simpler method which can be initiated in the clinical area and which does not necessitate calling in staff out of hours. Dialysate (2–3 ml) is aspirated from the bag and inoculated into thioglycollate broth with 5% CO_2 under vacuum (Gibco Ltd), which is then sent to the laboratory for appropriate subculture. Using this technique we isolated organisms from 84% of specimens (Knight *et al.*, 1982); since then this method has given a consistently high positive culture rate (87%) which compares well with the 79% reported by Fenton (1982).

We would also like to mention our experience with treating peritonitis with oral cephradine. Encouraged by a preliminary study (Knight *et al.*, 1982) we went on to treat 58 episodes of peritonitis alternately with oral cephradine or intraperitoneal cefuroxime for 7 days. The primary resolution rate was not significantly different in the two groups (66% with oral cephradine, 55% with cefuroxime). We have since adopted a 7-day course of oral cephradine 500 mg 6-hourly as our standard empirical treatment. We have, to date, treated 168 episodes in this way with a clinical response in 101 (60%). There was secondary success with an alternative drug in 43 episodes (26%); intractable peritonitis leading to catheter loss occurred in 24 (14%). We have had no episodes of cephalosporin-related diarrhoea, possibly because we restrict the course to 7 days. We agree with Spencer & Fenton (1984) that the optimum length of treatment remains still to be determined, but in a condition caused by endogenous infection with commensal flora, it seems logical to aim for the shortest course which is clinically effective, thus causing minimal interference with the balance and antimicrobial sensitivity of the potential pathogens.

Prevention of peritonitis is obviously the desirable objective. Gruer and his colleagues (1984) report that they were able to reduce the incidence of peritonitis due to coagulase-negative staphylococci by a double alcohol handwash before bag changing. Perhaps the time has come for a trial of gloves—a real reduction in peritonitis might outweigh the additional expense.

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Sir,

Peritonitis in CAPD patients

Raman & Maskell (1985) incorrectly state that we found the incidence of CAPD peritonitis was reduced by a double-alcohol wash before bag changing. The double-alcohol wash was indeed much more effective than povidone-iodine in reducing the resident flora of the hands. The incidence of peritonitis caused by coagulase-negative staphylococci did fall during the study period. However, the reduction was common to both the alcohol and the povidone-iodine using groups. After the study, the incidence of coagulase-negative staphylococcal peritonitis rose quickly to pre-study levels—although by then all patients were using the double-alcohol wash! We suspect the temporary improvement occurred because patients were aware their bag changing technique was under scrutiny during the study and therefore became more diligent. We await the development of a truly secure method of bag-changing which keeps hands and connectors well apart. The recently described sterile weld system looks promising (Hamilton *et al.*, 1983).

I agree with Raman & Maskell (1985) that the pour-plate culture technique described by Fenton (1982) fails, as does filtration, because it requires the presence of skilled laboratory staff from the outset. At the Queen Elizabeth Hospital, Birmingham, a simple bottle culture technique, similar to that described by Raman & Maskell (1985), is used. Once inoculated, the bottles were treated like blood cultures. Over the first 2 years, organisms were cultured by this method in 89% of 148 episodes of CAPD peritonitis. Simultaneous plate culture of a centrifuged deposit was useful only for isolating certain strict aerobes such as *Agrobacterium* spp, and raised the total isolation rate to 95% of episodes.

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ONCE-DAILY ANTIBIOTIC TREATMENT OF CAPD PERITONITIS

SIR,—Peritonitis remains the main threat to successful continuous ambulatory peritoneal dialysis (CAPD). We have attempted to develop a treatment policy that has a sound microbiological base, but which can be used easily by the patient treating himself at home. A study of the antibiotic sensitivities of organisms isolated from infected dialysis specimens over one year showed that the most reliable initial treatment would be a combination of vancomycin[1] and an aminoglycoside.

The treatment policy adopted was as follows. After samples of dialysate fluid have been taken for microscopy and culture, 100 mg vancomycin and 40 mg gentamicin are added to the next bag of dialysis fluid. Patients who are not seriously ill are then allowed home with instructions to add 100 mg vancomycin and 40 mg gentamicin to subsequent overnight bags only. When the results of culture are known (generally after 48 h), it is usually possible to continue with one antibiotic only. Treatment is continued for 10 days. Patients with significant systemic evidence of infection are also given an initial intravenous dose of vancomycin 500 mg and gentamicin 40 mg.

Results of treatment of the first 100 consecutive episodes were:

—	*No*
Bacteriological findings:	
Culture positive episodes	83
Gram-positive strains (100% vancomycin sensitive)	74
Gram-negative strains (66% gentamicin sensitive)	18
Cure achieved with:	
Once-daily treatment only	88
Extended course of vancomycin	4
Other antibiotics	6
After catheter removal	2
Home/hospital treatment	
Episode treated entirely at home	79
Overnight stay only	7
Admission because of peritonitis	8
Admission for other reasons	6

Most patients successfully treated themselves at home without altering their dialysis routine. Only two patients required a temporary removal of the peritoneal catheter. No clinical side-effects of the antibiotics were seen. Peak serum levels were 5·5 to 12 mg/l for vancomycin and less than 3 mg/l for gentamicin. The adoption of this policy has greatly simplified our treatment of peritonitis, increasing our cure rate and decreasing the incidence of antibiotic-associated colitis, which had been a feature of our previous treatment regimen with cephalosporins. The simplified regimen has been welcomed by patients and staff alike.

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Vancomycin and Tobramycin in the Treatment of CAPD Peritonitis

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Key Words. CAPD · Peritonitis · Vancomycin · Tobramycin

Abstract. Seventy-five episodes of continuous ambulatory peritoneal dialysis (CAPD) peritonitis were studied during a 1 year period at the Queen Elizabeth Hospital, Birmingham. When two simple culture methods were used in parallel, the causative organisms were identified in 97% of cases. Nearly two thirds of episodes of peritonitis were caused by coagulase-negative staphylococci (C-NS), many of which were multiply antibiotic-resistant. On the basis of detailed antibiotic sensitivities, intraperitoneal vancomycin and tobramycin were chosen for the initial treatment of CAPD peritonitis. With this regime, a cure was achieved in 32 of 38 episodes, compared with 15 of 27 episodes when cefuroxime was used. All but 1 of 24 episodes caused by C-NS were cured by vancomycin.

Introduction

Infective peritonitis remains the major complication of continuous ambulatory peritoneal dialysis (CAPD) [1–6]. Most centres report two obstacles to effective treatment. Firstly, the causative organism cannot be identified in 15–40% of episodes. Secondly, multiply antibiotic-resistant organisms are commonly encountered. Using a novel method of culture, we have been able to identify the causative organism in almost all cases. We describe an antibiotic policy based on an analysis of the antibiotic sensitivities of isolates obtained over a 1-year period and show how its use has led to a reduction in morbidity from CAPD peritonitis.

Patients and Methods

This study included all episodes of peritonitis occurring in 39 patients on CAPD at the Queen Elizabeth Hospital between March 1, 1982 and February 28, 1983. The age range of the patients was from 16 to 65 years, with a mean of 39(± SD) 13 years. There were 26 males and 13 females. Ten of the 39 patients were diabetics. All the patients were on 3 or 4 exchanges of dialysate/day.

Microbiological Investigations

Eighty millilitres of dialysis effluent were removed aseptically from the waste bag. Twenty millilitres were placed in a sterile universal container. The remaining 60 ml were injected via a fresh sterile needle into a standard 100-ml medical flat bottle containing 20 ml of sterile nutrient broth (Oxoid No.2) at 4 times normal strength, thereby diluting it to the correct concentration. During normal working hours all samples were then sent directly to the laboratory. At other times, the universal container was kept in a refrigerator at 4 °C and the dialysate culture bottle in an icubator at 37 °C until the laboratory opened. Bacterial peritonitis was considered to be present if more than 100 neutrophil polymorphs/mm^3 were seen. The fluid in the universal container was centrifuged and the deposit used to prepare a gram-stained film and to inoculate blood and CLED agar plates for aerobic incubation. The culture bottle was incubated aerobically and subcultured after 24 h onto blood agar for both aerobic and anaerobic incubation, or if growth was detected visually, at any time during the next 9 days. Isolates were identified using conventional techniques. Antibiotic sensitivities were determined using the Stokes disc diffusion method [7]. In addition, a standard agar plate dilution method [8] was used to determine the minimum inhibitory cencentration (MIC) of 13 antibiotics against isolates of coagulase-negative staphylcocci (C-NS).

Initial Antibiotic Therapy

Two regimes were used in the course of the study. In each case, treatment was started as soon as bacteriological samples had been taken.

Regime 1 (March–September 1982): An initial dose of cefuroxime 500 mg intravenously followed by cefuroxime 75 mg/l of dialysate for 12 days. If isolates were resistant to cefuroxime, another appropriate antibiotic was used.

Regime 2 (October 1982–February 1983): an initial dose of vancomycin 500 mg intravenously followed by vancomycin 15 mg/l of dialysate and tobramycin 8 mg/l of dialysate. After 48–72 h, the antibiotic treatment was adjusted in the light of the bacteriological results as follows: (1) vancomycin-sensitive organisms: vancomycin 15 mg/l of dialysate for 12 days; (2) vancomycin-resistant, tobramycin-sensitive organisms: tobramycin 8 mg/l for 12 days; (3) organisms resistant to both vancomycin and tobramycin: another appropriate antibiotic for 12 days; (4) if no organism was cultured in the face of a clinical diagnosis of peritonitis, both antibiotics were continued for 12 days.

In all except 6 epidodes of peritonitis the patients were treated at home; they continued, their usual dialysis schedule and added antibiotics to their dialysate. Six patients were admitted because they were clinically unwell with a peritonitis. These patients were treated with intermittent peritoneal dialysis for 72 h, using an automatic cycler. Antibiotics were added to the dialysate in the same doses as in those patients on CAPD.

Antibiotic Concentrations

Serum vancomycin concentrations were assayed using an Abbott TDX immunoassay system (Abbott Diagnostics Division, Queensborough, Kent, UK). Serum tobramycin concentrations were assayed using an EMIT immunoassay system (Syva UK. Ltd, Maidenhead, Berks., UK).

Statistics

The statistical significance of differences was tested by the χ^2 test with Yates correction.

Results

Microbiology of the Effluent

During the 12 months from March 1, 1982 to February 28, 1983, 75 episodes of acute peritonitis occurred during 286 patient-months of CAPD. Organisms were isolated from the effluent in 71 of the 75 episodes (95%). One species was cultured on 66 occasions and two on 5 occasions. Table I shows that C-NS were isolated on 44 occasions (62%), whereas no other organism was cultured on more than 4 occasions.

In 71 of the 75 episodes, both bottle and plate methods were used, and organisms were isolated on 69 occasions (97%). In the other 4 episodes, only the plate method was used and organisms were cultured on 2 occasions. Eighteen (24%) of organisms were isolated by the bottle method alone, and 10 (13%) by the plate method alone. The bottle method isolated significantly more C-NS than the plate method (41:31, $p < 0.01$), whilst 7 gram-negative bacilli (***Acinetobacter anitratus, Proteus mirabilis, Agrobacterium*** sp., ***Enterobacter cloacae,*** and 3 unidentified aerobic gram-negative bacilli) were cultured only by the plate method. The two methods thus seemed complementary.

Table I. Bacteria isolated from dialysis effluent during 71 episodes of CAPD peritonitis

Organism	Number of isolates	
Coagulase-negative staphylococci	44	
Other gram-positive organisms	10	
Streptococcus viridans		4
Streptococcus faecalis		3
Staphilococcus aureus		2
Diphteroid		1
Gram-negative bacteria	22	
Klebsiella aerogenes		4
Enterobacter spp.		4
Acinetobacter spp.		3
Pseudomonas aeruginosa		3
Serratia marcescens		2
Escherichia coli		1
Proteus mirabilis		1
Agrobacterium sp.		1
Other aerobic gram-negative bacilli		3
Total	76	

Antibiotic Sensitivities

Coagulase-Negative Staphylococci. Full details of the antibiotic sensitivities of the strains of C-NS isolated during the study have been published elsewhere [8]. Only vancomycin was active against all strains. Netilmicin, rifampicin and cefamandole were active against at least 95% of strains. However, 16 of the 41 strains tested (40%) were highly resistant to cefuroxime (MIC $\geq$ 32 mg/l).

Other Gram-Positive Organisms. Only those 4 antibiotics consistently active against the C-NS were tested against the 10 other gram-positive (table I). Vancomycin and rifampicin were active against all 10 isolates, cefamandole was active against all except the ***Streptococcus faecalis*** isolates, netilmicin was active only against the *Staphylococcus aureus* and diphtheroid isolates.

Overall activity of the 4 antibiotics against gram-positive isolates was therefore: vancomycin 100%, rifampicin 98%, cefamandole 91% and netilmicin 85%.

Gram-Negative Organisms. Of the 4 antibiotics most active against gram-positive organisms, only netilmicin was also consistently active against gram-negative organ-

Table II. Overall sensitivities of 76 isolates from effluent from CAPD patients with peritonitis

Antibiotic	Number of sensitive isolates	Number of resistant isolates	Sensitive isolatess, %
Vancomycin and netilmicin	73	3	96
Vancomycin and gentamicin/tobramycin	72	4	95
Netilmicin	65	11	86
Cefamandole	56	20	74
Cefuroxime	36	40	47

isms, inhibiting all but 3 of the 22 isolates, ***Klebsiella aerogenes*, *Agrobacterium*** sp. and an unidentified aerobic gram-negative bacillus. Other antibiotics which were found to be active against most isolates were gentamicin and tobramycin (18 of 22) and cefotaxime (16 of 22). Cefuroxime and cefamandole were only active agaisnt 7 of 22 isolates.

Overal Antibiotic Sensitivites. These are shown in table II. The best single agent was netilmicin, active against 86% of isolates. However, combinations of vancomycin and netilmicin and vancomycin and tobramycin/gentamicin were active against 96 and 95% of isolates, respectively. Cefuroxime, our drug of choice at the start of the study, was active against only 47% of isolates.

Antibiotic Treatment

During the first 7 months of the study, 15 of 27 episodes of CAPD peritonitis (56%) were successfully treated with cefuroxime alone. Only 6 of the 14 episodes caused by C-NS responded. Eleven of the 12 unresponsive.infections were subsequently successfully treated with either vancomycin or tobramycin. In 1 case, the patient only recovered after removal of the intraperitoneal catheter.

In the light of these results and the antibiotic sensitivity data which had accumulated during the first 6 months of the study, we changed our initial treatment from cefuroxime to a combination of vancomycin and tobramycin.

During the final 5 months of the study, 32 of 38 episodes (84%) were successfully treated with vancomycin and tobramycin. Twenty-three of the 24 episodes caused by C-NS responded to vancomycin compared with 6 of 14 treated with cefuroxime ($p < 0.001$). The organisms causing the 6 episodes which did not respond to vancomycin and tobramycin were ***K. aerogenes*; *P. mirabilis*; *Pseudomonas aeruginosa*** and ***S. aureus*; *Agrobacterium*** sp.; a diphtheroid; and a C-NS. These infections did not respond to other antibiotics and were only cured by removal of the intraperitoneal catheter.

Vancomycin and Tobramycin Concentrations

Serum vancomycin and tobramycin concentrations were each measured in 6 patients after 5-14 days treatment. Vancomycin concentrations ranged from 8 to 12 mg/l (mean 10.1 mg/l) and tobramycin concentrations from 3.1 to 4.8 mg/l (mean 3.6 mg/l).

Discussion

In most published surveys of CAPD peritonitis, a causative organism could not be isolated in at least 15% of cases [1-5]. Until now, only *Vas* et al. [6] using expensive and complicated filtration techniques, have reported an isolation rate of over 90%. The methods we have described are simple and cheap and have the added advantage that samples do not need to be processed outside normal laboratory hours. CAPD dialysate is not a good culture medium and hence any bacteria present may be both few in number and in poor condition. The bottle culture method allows a large volume of fluid to be cultured without subjecting the organisms to the additional stresses of centrifugation or filtration. It appears to be particularly suitable for isolating C-NS.

We isolated C-NS from 62% of 71 culture-positive samples. This is a higher proportion than that reported in other series [1-6], and may in part reflect the sensitivity of our culture methods. C-NS were also responsible for several prolonged episodes of peritonitis despite treatment with cefuroxime, our antibiotic of choice at the start of the study. Our efforts to formulate a policy for the initial treatment of CAPD peritonitis therefore centred on this group of organisms.

Only vancomycin was active against all the C-NS isolates tested. Several other authors also report that C-NS causing CAPD peritonitis are consistently sensitive to vancomycin but often resistant to many other antibiotics [2, 9-11]. Vancomycin and rifampicin were also consistently active against the other gram-positive isolates from our patients but several streptococci were resistant to netilmicin and cefamandole. Setting aside rifampicin because of its status as an anti-tuberculous drug and because rifampicin-resistant mutants can readily occur [12], vancomycin emerged as clearly the best antibiotic for treating gram-positive organisms. On the other hand, the aminoglycosides – netilmicin, tobramycin and gentamicin – had the most consistent activity against the gram-negative isolates. There was therefore no single antibiotic which could be used with confidence in the initial treatment of CAPD peritonitis but a combination of vancomycin and an aminoglycoside appeared to provide nearly total cover. Despite the slightly wider activity of netilmicin, we felt that its use was best restricted, since it is more expensive than tobramycin or gentamicin and useful as an antibiotic reserved for treating serious infections caused by gram-negative bacilli resistant to gentamicin and tobramycin. We therefore chose to use tobramycin, which at that time was cheaper than gentamicin.

During the first 7 months of the study we attempted to treat CAPD peritonitis with cefuroxime at a dose of 75 mg/l of dialysate. Only 15 of 27 (56%) episodes of peritonitis were cured with this treatment. It could be argued that the dose of cefuroxime used was too low to be effective. However we found that 40% of the C-NS tested were highly resistant to cefuroxime with MIC. $\geq$ 32 mg/l. In other studies using cefuroxime in doses of up to 200 mg/l of dialysate, a similar failure rate was observed [2, 4]. During the final 5 months of our study, vancomycin and tobramycin successfully cured 84% of 38 episodes of peritonitis, including all but 1 of 24 episodes caused by C-NS.

The use of vancomycin and tobramycin has thus led to a substantial improvement in the results of our treatment of CAPD peritonitis. Both drugs, however, carry the risk of ototoxicity. If they are to be generally used for treating CAPD peritonitis, it is essential that this risk be minimised. Current preparations of vancomycin have been associated with a very low incidence of ototoxicity and then only when serum levels exceed 80 mg/l [13]. Our regime led to serum levels around 10 mg/l, which are unlikely to be hazardous. On the other hand, we found that serum tobramycin levels were generally between 3 and 5 mg/l. Similar results have been reported elsewhere [14, 15]. Tobramycin and gentamicin appear equally ototoxic in humans [16]. *Maer* [17] has provided evidence that the risk of ototoxicity increases markedly when the product of the mean serum trough concentration of gentamicin (mg/l) and duration of treatment exceeds 45. This figure undoubtedly was exceeded in some of our patients, although ototoxicity was not clinically apparent. Consequently, we are studying the use of intermittent doses of intraperitoneal vancomycin and aminoglycosides in a attempt to reduce antibiotic concentrations whilst preserving antimicrobial efficacy.

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